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References:
Hauser & Hudson. Organic Reactions, **1942**, 278.
Bachman, Cole & Wilds, J.A.C.S. **62**, 835.
Fisher & McElvain, J.A.C.S. **56**, 1766.
Komppa. Ann. **368**, 137.

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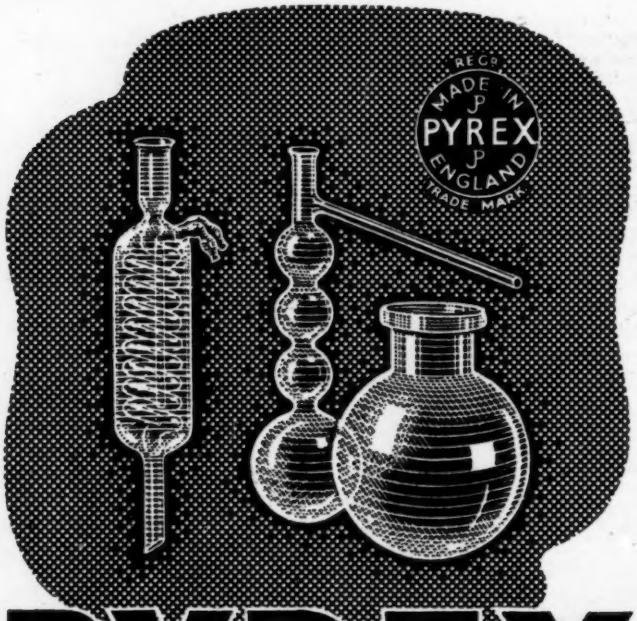

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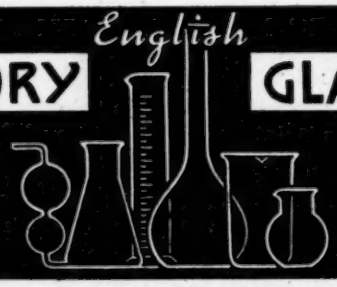

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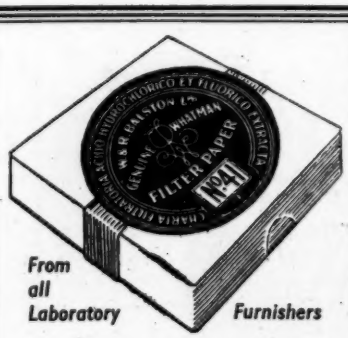

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removed, and the residue then crystallised from ethylene dichloride, acetone, or other suitable solvents. The results are summarised in the following table.

Amine (0·1 g.-mol.).	Deaminated product.	Yield, g.	Yield, %.
2 : 4-Dinitro-1-naphthylamine	1 : 3-Dinitronaphthalene	18·0	82·0
4-Chloro-2-nitro-1-naphthylamine	1-Chloro-3-nitronaphthalene	15·4	75·0
4-Bromo-2-nitro-1-naphthylamine	1-Bromo-3-nitronaphthalene	19·0	75·5
2-Nitro-1-naphthylamine	2-Nitronaphthalene	12·2	70·0
4-Nitro-1-naphthylamine	1-Nitronaphthalene	11·8	68·0
2-Naphthylamine	Naphthalene	6·0	47·0
3-Nitro-4-toluidine	3-Nitrotoluene	5·3	39·0
2 : 5-Dichloroaniline	1 : 4-Dichlorobenzene	5·0	35·0
2-Nitroaniline	Nitrobenzene	3·5	28·0
2-Nitro-4-toluidine	2-Nitrotoluene	3·56	26·0
p-Toluidine	Toluene	2·2	24·0
Benzidine	Diphenyl	3·5	23·0
p-Nitroaniline	Nitrobenzene	2·68	21·6
Aniline	Diphenyl (only a trace of benzene)	2·0	26·0

The authors thank I.C.I. Ltd., Dyestuffs Division, for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, December 1st*, 1943.]

NOTE.

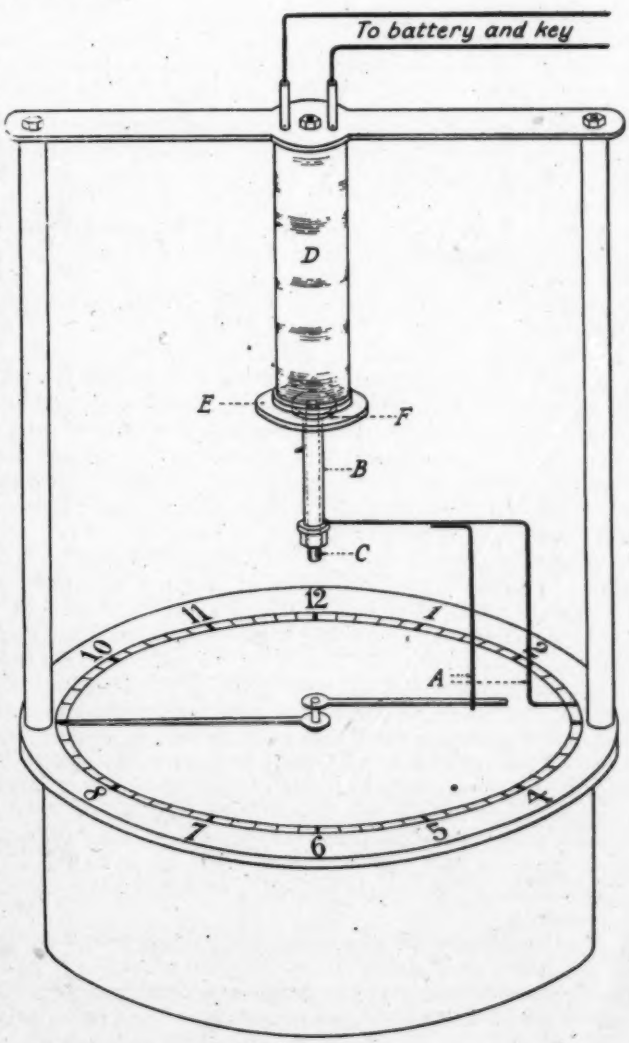
A Laboratory Timing Clock. By GILBERT F. SMITH.

THE usual type of stop-clock records the time interval between two events with an accuracy of at least 1 sec., but is less accurate if a large number of successive events have to be timed while the clock is going. The clock now described does not suffer from this disadvantage and allows the timing of any number of successive events to about ½ sec.

An electric clock of sufficient power to turn a 12" hand is required. The glass and the hour hand are removed, and the second hand is slightly shortened and provided with a rider *A* (see fig.) made of stiff steel wire. One prong of the rider serves as a pointer to indicate seconds on the scale, and the other engages on the forward edge of the seconds hand. The rider can rotate coaxially with the seconds hand and can also move upwards sufficiently far to disengage from the hand. To obtain these motions the rider is soldered to a brass tube *B*, which is a sliding fit over a thin steel rod *C*, and this is itself fixed firmly into a hole drilled into the centre of the lower face of a 6-volt electromagnet *D*, suspended as shown over the centre of the clock. A thin iron disc *E* is soldered round the top of tube *B*. By means of the hexagon nut at the bottom of the steel rod the rider assembly is adjusted so that the disc *E* is clear of the lower face *F* of the electromagnet.

When the clock is running, the seconds hand drives the rider round in front of it. In order to take a reading the electromagnet is energised by completing the electric circuit by means of a tapping key. This raises the rider clear of the hand and at the same time stops it, so that the reading given by the pointer can be made at leisure. The clock is ready for a second reading when the key is released and the rider is turned backwards by means of the iron disc to re-engage with the oncoming hand. At least four readings per minute can easily be made. The clock is used lying horizontally, and any tendency of the rider to overrun the hand is avoided by using a stiff lubricant, such as vaselin, in the rider bearing.

A clock of this type has been in use in these laboratories for several years, and despite its simple construction, it has never given trouble. It has been extremely useful in measuring the relatively small time intervals which are often required in experiments on chemical kinetics.—THE UNIVERSITY, LEEDS. [*Received, January 5th*, 1944.]



43. *Rubber, Polyisoprenes, and Allied Compounds. Part VI. The Mechanism of Halogen-substitution Reactions, and the Additive Halogenation of Rubber and of Dihydromyrcene.*

By George F. Bloomfield.

The chlorination of *cyclo*hexene by chlorine or by sulphuryl chloride (in the absence of a peroxide catalyst) yields substituted as well as additive chlorination products, and the former retain in full the original olefinic unsaturation as indicated by iodine-value determination; but whereas sulphuryl chloride forms only the additive dichloride and a monochloro-olefin which is substituted exclusively in the 3-position, yet chlorine yields a mixture of saturated trichloro-derivative (chloro-substituted addition product) and isomeric monochloro-olefins (3- and 4-substituted), together with some additive dichloride.

No evidence of substitution at the ethylenic methine carbon atom has been obtained in the chlorination of *cyclo*hexene, dihydromyrcene, and rubber by chlorine. The diminished unsaturation of the chloro-substitution products of the last two hydrocarbons is attributed to cyclisation—a process which is complete in the case of rubber, but affects only a minor proportion of the molecules of dihydromyrcene. The same cyclising tendency appears in the substitutive bromination of rubber by *N*-bromosuccinimide, but not to any appreciable extent in the similar bromination of dihydromyrcene.

Additive chlorination products are formed when rubber is brought into reaction with chlorine liberated by the thermal dissociation of phenyliododichloride, or of sulphuryl chloride in the presence of a peroxide. The mode of reaction of bromine with rubber, about which many contradictory statements have been made, is found to be entirely additive if the solvent contains a trace of alcohol and the temperature is 0°. A method based on bromine addition may be used for estimating rubber hydrocarbon. Additive bromo- and chloro-derivatives of rubber are comparatively stable and give no indication of the spontaneous elimination of halogen acid either through cyclisation reactions or the re-formation of double bonds at temperatures up to 80°.

The provision of chlorine in free-radical form appears to be an essential condition for obtaining the wholly additive chlorination of rubber and allied olefins. The reaction of molecular chlorine or bromine, on the other hand, follows a course which can be adequately explained by the initial formation of an activated dihalide, the fate of which is determined by the nature of the olefinic system and the experimental conditions.

The chlorination of rubber presents a peculiar feature in that the observed unsaturation of the substitutive chlorination products is considerably lower than would be anticipated for a purely substitutive mode of reaction by the halogen (cf. Part IV, J., 1943, 289). The possible exercise by the substituent chlorine atoms present in the groups –CHCl·C:C– or –CH_2·CCl:C– of an inhibiting influence on the additive capacity of the double bond can be investigated by examination of halogenated derivatives of rubber and of allied olefins in which the position of the substituent halogen can be established. The work of Ziegler *et al.* (*Annalen*, 1942, **551**, 80) has not only drawn attention to an admirable reagent (*N*-bromosuccinimide) for the halogenation of olefins in the 3-position, but has also provided a method for estimating 3-substituted bromine by interaction with alcoholic silver nitrate.

The Action of Chlorine on cyclo*Hexene.*—The chlorination of *cyclo*hexene appeared to be particularly well suited for examining the details of the chlorination process as it occurs in simple olefins. The behaviour of *cyclo*hexene towards chlorine, however, differed from that of the olefins studied in Part IV in that, although the overall chlorination reaction was mainly substitutive (59%, thus giving monochloro*cyclo*hexene together with trichloro*cyclo*hexane in which both substitution and addition of chlorine had occurred), yet the major product was the additive dichloride, dichloro*cyclo*hexane. The monochloro*cyclo*hexene had the correct iodine value when allowance was made for the presence of a small proportion of dichloro*cyclo*hexane from which the chloro-olefin not could be completely freed.

Although peroxide-catalysed chlorination by sulphuryl chloride is normally additive in habit (Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 3432), it was found that *cyclo*hexene could none the less be chlorinated in a partly substitutive manner by this reagent if brought to reaction in the presence of an antioxidant or a halogen carrier. The resulting chloro*cyclo*hexene again had the correct iodine value, but whereas all of the chlorine in this chloro-olefin could be removed by a brief treatment with alcoholic silver nitrate, only 80—85% of the chlorine was similarly removed from the chloro*cyclo*hexene resulting from the action of chlorine on *cyclo*hexene (see table).* Now, since only an insignificant proportion of the chlorine in 1-chloro*cyclo*hexene, and only a relatively small proportion of that in monochloro*cyclo*hexane were removable by comparable treatment with silver nitrate, and, further, since 1-chloro*cyclo*hexene was found to add iodine chloride very incompletely, doubtless owing to the inhibiting effect of the 1-substituted chlorine (cf. dichloroethylene), it must be concluded that the chloro*cyclo*hexene resulting from chlorination by sulphuryl chloride is wholly 3-chloro*cyclo*hexene, whereas that resulting from the chlorination by chlorine is a mixture of this (*ca.* 80%) with a smaller proportion (*ca.* 20%) of an isomer, likely to be 4-chloro*cyclo*hexene, but containing no 1-chloro*cyclo*hexene. (The 4-chloro*cyclo*hexene is present in slightly greater proportion in the more volatile fractions of the mixture of isomers.)

Unsaturation of Halogen-substituted Polyisoprenes.—On the assumption that the above considerations apply to the chlorination of dihydromyrcene and of rubber, it must be considered highly improbable that the diminished iodine value observed for mono- and di-chloro-substituted dihydromyrcene and for monochloro-substituted rubber can be attributed to an inhibiting effect of the substituent chlorine atom, and hence cyclisation must be

* Additive dichlorides were comparatively stable to the silver nitrate reagent.

accepted as the most probable alternative cause. This view finds support in the behaviour of the afore-mentioned substituted derivatives of dihydromyrcene and of rubber towards silver nitrate (see table).

Reaction of Some Halogenated Substances with Alcoholic Silver Nitrate.

Substance.	Method of preparation.	$100 \times \frac{\text{Reactive halogen}}{\text{Total halogen}}$.
Chloro*cyclo*hexene, C_6H_9Cl	Cl_2 + *cyclo*hexene	80—85
,, ,,	SO_2Cl_2 + *cyclo*hexene + antioxidant	100
1-Chloro*cyclo*hexene, C_6H_9Cl	PCl_5 + *cyclo*hexanone	3
Chloro*cyclo*hexane, $C_6H_{11}Cl$		8
Bromo*cyclo*hexane, $C_6H_{11}Br$		99
Dichloro*cyclo*hexane, $C_6H_{10}Cl_2$	SO_2Cl_2 + *cyclo*hexene + peroxide	1
Chlorodihydromyrcene, $C_{10}H_{17}Cl$	Cl_2 + dihydromyrcene	85—90
Bromodihydromyrcene, $C_{10}H_{17}Br$	*N*-Bromosuccinimide + dihydromyrcene	99
Dihydromyrcene dichloride, $C_{10}H_{18}Cl_2$	SO_2Cl_2 + dihydromyrcene + peroxide	15
Chlororubber, $(C_{10}H_{15}Cl)_n$	Cl_2 + rubber	88
,, $(C_5H_7Cl)_n$	,, ,,	70
,, $(C_{10}H_{15}Cl)_n$	SO_2Cl_2 + rubber + antioxidant	90
Bromorubber, $(C_{10}H_{15}Br)_n$	*N*-Bromosuccinimide + rubber	94
Rubber dichloride, $(C_5H_8Cl_2)_n$	SO_2Cl_2 + rubber + peroxide	6

If the small proportion of the chlorine in these derivatives which is unreactive to silver nitrate is attributed to 1-substituted products, then the amount of these is quite insufficient to account for the whole of the observed lowering of iodine value; indeed, it seems more justifiable, as in the case of *cyclo*hexene, to attribute the unreactive part of the chlorine to substitution in positions other than the methinic and α-methylenic carbon atoms (*i.e.*, to substitution in the β- or β′-positions) and such substitution would cause no lowering of the iodine value. Furthermore, monobromodihydromyrcene obtained by the action of *N*-bromosuccinimide on dihydromyrcene has almost the theoretical iodine value (cf. low iodine value of monochlorodihydromyrcene obtained by the action of chlorine on dihydromyrcene), and all of its halogen is removed by silver nitrate.* The behaviour of the bromo-rubber similarly obtained is not, however, so satisfactory, its iodine value being considerably lower than that required for simple bromine-substitution. Since there is no justification for assuming that the mode of reaction of *N*-bromosuccinimide should be any different in the case of rubber from that established with the considerable number of olefins which have been successfully brominated at the α-methylenic position, this reduction of unsaturation is again attributed to cyclisation.

The further chlorination of monochloro-substituted rubber provides evidence in support of a cyclised structure. Reference has already been made in Part IV to the additive uptake of only 0·5 mol. of chlorine per C_5H_7Cl unit, which is in accordance with the observed unsaturation. It is now found that an excess of sulphuryl chloride reacting under additive conditions in the presence of a peroxidic catalyst also brings about the addition of only 0·5 mol. of halogen, the rest reacting substitutively. It is therefore concluded that the chlorination of polyisoprenes is particularly prone to proceed by a cyclisation mechanism. The cyclisation appears to be complete with rubber (leaving $|_1^=$ per two C_5H_7Cl units) but only partial with dihydromyrcene (*ca.* 30% of molecules cyclised); no separation of cyclised and uncyclised portions is practicable owing to the proximity of boiling points.

Formation of Polychloro-derivatives in Chlorination Reactions.—Although the ratio of liberated hydrogen chloride to reacted chlorine permits of the formation of only a monosubstituted chloro-derivative from rubber, the possibility of tri- or poly-chloride formation as well as additive chlorination must be taken into account when this ratio falls below unity. In the case of *cyclo*hexene the formation of a considerable proportion of trichloro*cyclo*hexane has been established, the relative proportions of the chlorination products from this olefin being dichloro*cyclo*hexane 47%, trichloro*cyclo*hexane 23%, 3-chloro*cyclo*hexene 19%, 4-chloro*cyclo*hexene 5%, residue (containing much chlorine) 6%. 1-Methyl*cyclo*hexene appears to yield mainly monochloromethyl*cyclo*hexene and trichloromethyl*cyclo*hexane with relatively little dichloromethyl*cyclo*hexane. Where these polychloro-derivatives are formed the yield of monochloro-olefin is considerably less than would be expected from the proportion of hydrogen chloride formed, *e.g.*, the simultaneous progress of reactions (1) and (2)

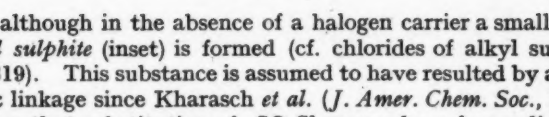
$$RH|_1^= + Cl_2 \longrightarrow RCl|_1^= + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$RH|_1^= + 2Cl_2 \longrightarrow RCl_3 + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

satisfies an overall reaction which is apparently 67% substitutive as measured by the hydrogen chloride : chlorine ratio, but the yield of monochloro-substitution product is only 33% when calculated on the amount of chlorine reacting.

Polychloride formation is greatest with *cyclo*hexene, even when the hydrocarbon is present in considerable excess; doubtless, the increase in monosubstitutive reaction in 1-methyl*cyclo*hexene, dihydromyrcene, squalene, and rubber is to be attributed to the influence of the 1-methyl substituent. No chloro-derivatives other than monochloro-olefin and additive dichloride are, however, obtained when sulphuryl chloride is used as a sub-

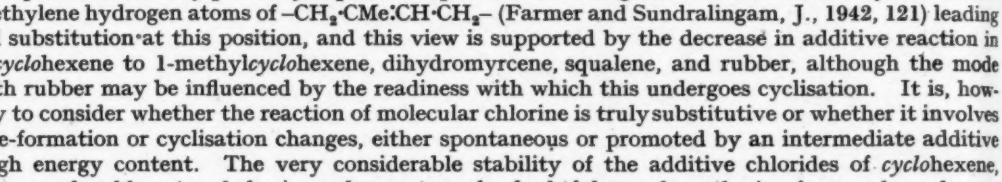
* The lability of substituted *bromine* towards alcoholic silver nitrate is, however, no certain criterion of the absence of substitution in the β-position, for, in contrast to the anticipated behaviour of the halogen in 4-chloro*cyclo*hexene, bromine located in the β-(or 4-) position may quite well be labile since the halogen in bromo*cyclo*hexane, unlike that in chloro*cyclo*hexane, is wholly reactive towards alcoholic silver nitrate.

stitutive chlorinating agent, although in the absence of a halogen carrier a small amount of the chloride of 2-*chlorocyclohexyl sulphite* (inset) is formed (cf. chlorides of alkyl sulphites, Stähler and Schirm, *Ber.*, 1911, **44**, 319). This substance is assumed to have resulted by addition of sulphuryl chloride to the ethylenic linkage since Kharasch *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 3089; 1940, **62**, 925, 2393) have shown that substitution of $-SO_2Cl$ groups by a free-radical chain mechanism leads to the formation of sulphonyl chlorides. Since the sulphur atom is linked to the carbon atom through oxygen the additive reaction is thought to pursue the molecular course :



The intermediate formation of the chloride of 2-chloro*cyclo*hexyl sulphite has been assumed by Friese and Djiang (*Ber.*, 1938, **71**, 667) to occur in the reaction of sulphuryl chloride with *cyclo*hexene and acetic acid, whereby 1-chloro-2-acetoxy*cyclo*hexene is isolated as a final product.

The reaction of chlorine with rubber and with allied olefins, which does not appear to follow a free-radical course since it proceeds with equal facility in darkness and in light and in the presence or absence of oxygen, antioxidants, or peroxides, is very probably dependent upon the activating effect of the –CMe:C– system on the left-hand α-methylene hydrogen atoms of $-CH_2{\cdot}CMe{:}CH{\cdot}CH_2-$ (Farmer and Sundralingam, J., 1942, 121) leading to preferential substitution at this position, and this view is supported by the decrease in additive reaction in passing from *cyclo*hexene to 1-methyl*cyclo*hexene, dihydromyrcene, squalene, and rubber, although the mode of reaction with rubber may be influenced by the readiness with which this undergoes cyclisation. It is, however, necessary to consider whether the reaction of molecular chlorine is truly substitutive or whether it involves double bond re-formation or cyclisation changes, either spontaneous or promoted by an intermediate additive chloride of high energy content. The very considerable stability of the additive chlorides of *cyclo*hexene, dihydromyrcene, and rubber (see below) renders extremely doubtful any hypothesis of secondary decomposition of an additive dichloride. The possibility of an induced decomposition of an additive dichloride (cf. decomposition of ethyl chloride in the presence of chlorine, Rust and Vaughan, *J. Org. Chem.*, 1940, **5**, 449) has been examined by submitting an additive dichloride of rubber to the action of chlorine; although some substitutive reaction occurred whereby the chlorine content was raised, there was no evidence of any significant elimination of hydrogen chloride other than that accounted for by the substitutively-reacting chlorine, nor was there evidence of any double bond re-formation. There still remains the possibility that reaction proceeds by a chain mechanism involving a resonance hybrid (Anantakrishnan and Venkataraman, *Chem. Reviews*, 1943, **33**, 27) or alternatively by formation of an activated additive dihalide of high energy content (Stewart *et al.*, *J. Amer. Chem. Soc.*, 1929, **51**, 3082 *et seq.*), deactivation of the latter proceeding in one or more of the following ways according to the prevailing reaction conditions, the energy associated with the activated dihalide, and the nature of the olefinic system :



Whether the halogenation reactions now under consideration are actually substitutive, or whether they proceed in accordance with the above hypotheses, cannot be finally established from the evidence available, but the bulk of the evidence rather favours a mechanism conforming with Stewart's proposals. The cyclisation mechanism (iii) seems somewhat preferable to that suggested in Part IV (scheme ii), since in the new scheme it is no longer necessary to assume a different point of attack of the halogen in the polyisoprene and *cyclo*hexene systems.

The Additive Halogenation of Rubber and of Dihydromyrcene.—It seemed desirable to examine some halogenation reactions in which the halogen is generated by decomposition of an easily dissociated halogeno-reagent. Phenyliododichloride is a suitable reagent for this purpose and has been shown by Garvey, Halley, and Allen (*J. Amer. Chem. Soc.*, 1937, **59**, 1827) to form additive chlorination products with *cyclo*hexene and other olefins. These workers have also shown that phenyliododifluoride reacts with rubber to give hydrogen fluoride and a monofluoro-rubber, the latter being formed either substitutively or by decomposition of an unstable difluoride. It was accordingly anticipated that phenyliododichloride would yield a monochloro-rubber and hydrogen chloride in the same way as chlorine itself, and indeed, Garvey *et al.* have stated generally that the mode of chlorination by this reagent is the same as that of chlorine. Surprisingly, this reagent has been found to halogenate rubber in an almost exclusively *additive* way, yielding a dichloride $(C_5H_8Cl_2)_n$ of considerable thermal stability compared with products of substitutive chlorination.

The chlorinating action of peroxide-catalysed sulphuryl chloride (cf. Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142) has already been used for the addition of chlorine at the ethylenic linkage of *cyclo*hexene (*idem*, *ibid.*, p. 3432), and this reagent has now enabled chlorine addition products to be obtained from dihydromyrcene and from rubber, although some difficulty was experienced in obtaining wholly additive reaction

with specimens of rubber which had not been submitted to careful purification to remove naturally occurring antioxidants.

The formation of a stable additive dichloride of rubber is of considerable theoretical interest, since a purely additive reaction free from substitution has not hitherto been achieved. An additive dibromide $(C_5H_8Br_2)_n$, on the other hand, was long ago prepared (Gladstone and Hibbert, J., 1888, **53**, 682; Weber, *Ber.*, 1900, **33**, 786), and indeed, attempts have been made to estimate rubber hydrocarbon by bromine addition, although the formation of the dibromide has not generally been accomplished without the liberation of some proportion of hydrogen bromide, and the dibromide when isolated has been reported to liberate hydrogen bromide vigorously at 50—60° (Weber, *loc. cit.*). Substitutive side reaction has, however, been minimised by operating at 0° in chloroform (Hinrichsen and Kindscher, *Z. anorg. Chem.*, 1913, **81**, 70).

A more detailed study of the manner of reaction of bromine with rubber appeared desirable, since it seemed to occupy an interesting intermediate position between the exclusively substitutive mode of reaction of chlorine and the exclusively additive mode of reaction of iodine chloride (Kemp, *Ind. Eng. Chem. Anal.*, 1934, **6**, 52). When rubber was acted upon by bromine at temperatures between 0° and − 40° no difficulty was experienced in obtaining exclusively additive reaction provided that some chloroform was present, and the bromide so obtained underwent no decomposition at all on heating to 80°, nor was there any evidence of change in unsaturation, such as might arise from double bond re-formation or from cyclisation, as a result of mild heat treatment of a partly brominated product. The effect of chloroform in suppressing substitutive reaction is probably due to traces of alcohol normally present in this solvent rather than to any special characteristic of the solvent itself, since addition of alcohol enabled bromination to be conducted in carbon tetrachloride without hydrogen bromide formation: in this connection it is of interest that an alcoholic medium has been found helpful in suppressing substitutive reaction in the preparation of dihydromyrcene tetrabromide (Schimmel's Report, Oct. 1911, 128).

In spite of statements to the contrary in the literature, bromine addition has in the present work been found satisfactory for estimating rubber hydrocarbon and has the special merit of speedy operation.

Mechanism of Additive Halogenation Reactions.—Kharasch and Brown (*J. Amer. Chem. Soc.*, 1940, **62**, 925) suggest that the twofold mode of reaction of sulphuryl chloride can be explained by the following hypotheses: (1) The peroxide-catalysed reaction furnishes a source of chlorine *atoms* and chlorination proceeds by a free-radical chain mechanism. (2) Thermal dissociation of the reagent provides some other form of active chlorine which reacts in the same way as chlorine itself. In the former case the reaction mechanism is of the same nature as that proposed for photochemical chlorination (Schumacher and Stauff, *Angew. Chem.*, 1936, **49**, 613; 1940, **53**, 501; *Z. Elektrochem.*, 1942, **48**, 271, 550), which even in a simple substitutive reaction may follow a course quite different from that promoted by chlorine in the absence of direct illumination, for whereas photochemical chlorination with chlorine (Michael and Garner, *Ber.*, 1901, **34**, 4046) and the peroxide-catalysed reaction of sulphuryl chloride both lead to substitution of fatty acids in the β-position (mainly), yet non-photochemical chlorination carried out with chlorine (Markownikow, *Annalen*, 1870, **153**, 241; Wolffenstein and Rolle, *Ber.*, 1908, **41**, 733) or with sulphuryl chloride in the presence of a halogen carrier yields α-substituted acids.

If these hypotheses are accepted in the present investigation, then, if it can be shown that chlorination by phenyliododichloride follows a free-radical course, there will be reason to think that the presentation of the chlorine in free radical (*i.e.*, atomic) form is also an essential condition for the additive chlorination of rubber and of allied olefins. Although the reaction with phenyliododichloride gave in practice no obvious sign of being peroxide-catalysed, there was evidence of an underlying free-radical chain mechanism in the fact that the reaction in the presence of quinol was very slow and incomplete and was also to a considerable extent substitutive in character. Zappi and Degiorgi (*Bull. Soc. chim.*, 1931, **49**, 1035; 1932, **51**, 1605) have differentiated between the electrical charges associated with the two chlorine atoms in phenyliododichloride, hence the separation of a free chlorine atom by thermal dissociation (equation 1) is not an unlikely initiating step, although in the presence of a peroxide the steps shown in equations 2—4 represent a more probable course of reaction. After

$$PhICl_2 \longrightarrow PhICl^{\bullet} + Cl^{\bullet} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Peroxide \longrightarrow R^{\bullet} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$R^{\bullet} + PhICl_2 \longrightarrow RCl + PhICl^{\bullet} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$PhICl^{\bullet} \longrightarrow PhI + Cl^{\bullet} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

the liberation of atomic chlorine the reaction could quite well proceed by the chain mechanism proposed for sulphuryl chloride (Kharasch and Brown, *loc. cit.*).

Attempts have been made to confirm the requirement of atomic chlorine for obtaining the additive chlorination of rubber by bringing chlorine into contact with a rubber solution which was irradiated by a powerful ultra-violet lamp, and also with a rubber solution containing benzoyl peroxide (the latter experiment being conducted at 80°), but in neither case was there any obvious departure from the usual exclusively substitutive reaction of the chlorine. Probably the substitutive reaction of molecular chlorine proceeds more readily than the additive reaction of free radical chlorine when both forms of the reagent are present.

An explanation of the substitutive bromination of olefins by *N*-bromosuccinimide presents rather more difficulty, but a chain mechanism of the type represented by equations 5—8 provides a satisfactory explanation if it be assumed that the major influence directing the reaction is the tendency of the $\begin{matrix}CH_2—CO\\CH_2—CO\end{matrix}\!\!>\!N^{\bullet}$ radical

(formed in the first instance by thermal dissociation of the bromo-compound) to accept hydrogen (6) and that the α-methylene hydrogen atom is the one most readily detached from the $-CH_2\cdot CR{:}CH-$ system.

$$(C_4H_4O_2)N\cdot Br \longrightarrow (C_4H_4O_2)N^{\cdot} + Br^{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$-CH_2\cdot C{:}C- + (C_4H_4O_2)N^{\cdot} \longrightarrow -\dot{C}H\cdot C{:}C- + (C_4H_4O_2)NH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

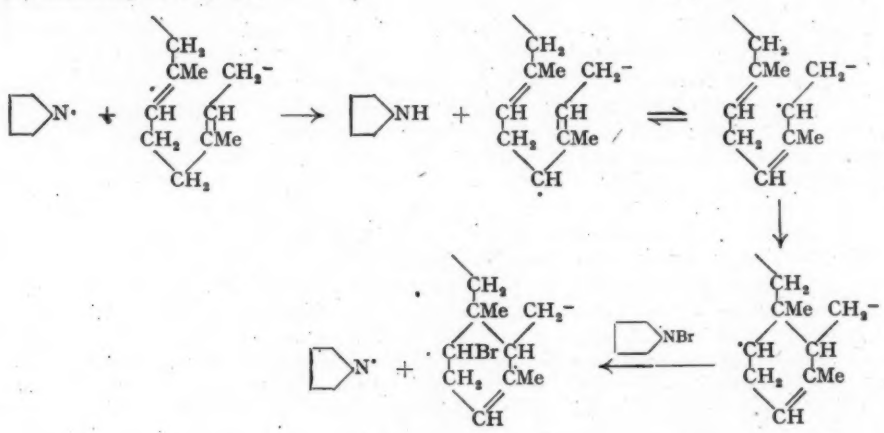
$$-\dot{C}H\cdot C{:}C- + Br^{\cdot} \longrightarrow -CHBr\cdot C{:}C- \text{ (or } -C{:}C\cdot CHBr-) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

(chain termination)

$$-\dot{C}H\cdot C{:}C- + (C_4H_4O_2)N\cdot Br \longrightarrow \underset{(\text{or } -C{:}C\cdot CHBr-)}{-CHBr\cdot C{:}C-} + (C_4H_4O_2)N^{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

(chain propagation)

The production of isomeric bromo-substituted products in reactions (7) and (8) (cf. Ziegler *et al.*, *loc. cit.*) is to be anticipated as a result of resonance in the $-\dot{C}H\cdot C{:}C-$ radical (Farmer, Koch, and Sutton, J., 1943, 541), and the very considerable degree of cyclisation promoted by the action of *N*-bromosuccinimide on rubber can be similarly explained by the following mechanism.



Experimental.

(Microanalyses were carried out by Dr. W. T. Chambers and Miss H. Rhodes.)

In general, the chlorination apparatus described in Part IV (Fig. 1) was used. For halogenating agents other than chlorine the graduated tube *A* was removed; liquid reagents were introduced beneath the surface of the rubber solution in *B*, and for this purpose a dropping funnel was fitted. A stirrer was also introduced into *B* to ensure thorough mixing of liquid and solid reagents. Gaseous reaction products were swept into an absorption system by means of a brisk stream of purified nitrogen which also prevented access of air to the reaction system.

Treatment of Halogenated Products with Alcoholic Silver Nitrate.—The sample (0·1 g.) was dissolved in a little alcohol, alcoholic silver nitrate (25 c.c., 0·1N) added, and the solution heated under reflux for 30 mins. After cooling, the solution was suitably diluted and an aliquot portion was added to an excess of sodium chloride solution (0·025N), the excess being estimated volumetrically with silver nitrate solution (0·025N), dichlorofluorescein being used as internal indicator.

Alcohol-insoluble substances (*e.g.*, halogenated rubbers) were dissolved in benzene (0·1 g. in 100 c.c.), and to the solution, warmed to 50—60°, was added a mixture (50 c.c.) of equal volumes of alcoholic silver nitrate (0·1N) and benzene. After refluxing for 1 hour and subsequently cooling, the solution was washed with successive small quantities of water until free from silver; the washings were combined, and an aliquot portion treated as above.

The proportion of the halogen which reacted with the silver nitrate, expressed as a % of the halogen in the sample, is hereinafter described as "reactive halogen."

Halogenation with Chlorine.

The Action of Chlorine on cyclo*Hexene.*—Peroxide-free *cyclo*hexene (20 c.c.; prepared by shaking with aqueous sodium hyposulphite, drying in an inert atmosphere, and distilling in a stream of purified nitrogen) was treated with chlorine (14·4 g.) at 80° in the absence of oxygen and in very subdued light: 4·33 g. of hydrogen chloride were formed, corresponding to 59% substitutive reaction. Distillation of the liquid product (26·2 g.) gave the following fractions: (i) unreacted *cyclo*hexene; (ii) b. p. < 40°/13 mm. (1·0 g.); (iii) b. p. 40—50°/13 mm. (2·0 g.); (iv) b. p. 50—60°/13 mm. (2·5 g.); (v) b. p. 60—68°/13 mm. (Found: *I.V.*, 31) (2·4 g.); (vi) b. p. 68—70°/13 mm. (Found: *I.V.*, 9) (1·6 g.); (vii) b. p. 70—72°/13 mm. (2·1 g.); (viii) b. p. 30—52°/0·01 mm. (2·1 g.); (ix) b. p. 52—53°/0·01 mm. (2·8 g.); (x) b. p. 53—60°/0·01 mm. (0·4 g.); (xi) small residue (1·0 g.). Fractions (viii)—(x) were saturated to iodine chloride and to bromine, (vi) and (vii) were mainly 1 : 2-dichloro*cyclo*hexane (cf. product of reaction of sulphuryl chloride with *cyclo*hexene, p. 119), and (ix) was a trichloro*cyclo*hexane (Found: Cl, 56·7. Calc. for $C_6H_9Cl_3$: Cl, 56·8%). The bulk of the unsaturated products were in the more volatile fractions; (iii) and (iv) were accordingly united and redistilled, yielding fractions (xii) b. p. 38—40°/13 mm. (1·2 g.); (xiii) b. p. 40—43°/13 mm. (1·5 g.); (xiv) b. p. 43—65°/13 mm. (0·6 g.); and (xv) b. p. 65—68°/13 mm. (1·2 g.). The last fraction was saturated to iodine chloride and was added to the dichloro*cyclo*hexane fractions. The foregoing separative procedure thus yielded the following main products: mono-chloro*cyclo*hexene (4·3 g.), dichloro*cyclo*hexane (8·4 g.), and trichloro*cyclo*hexane (4·2 g.). Fractions (xii) and (xiii) comprised the chloro*cyclo*hexene but were not entirely free from dichloro-derivatives [Found for (xii): C, 61·1; H, 7·75; Cl, 31·1; reactive Cl, 23·1; *I.V.*, 205. Calc. for a mixture of 95·5% C_6H_9Cl and 4·5% $C_6H_{10}Cl_2$: C, 61·1; H, 7·7; Cl 31·2%; *I.V.*, 208. Found for (xiii): C, 60·4; H, 7·7; Cl, 31·6; reactive Cl, 23·5; *I.V.*, 204. Calc. for a mixture of 91·8% C_6H_9Cl and 8·2% $C_6H_{10}Cl_2$: C, 60·65; H, 7·7; Cl, 31·75%; *I.V.* 200].

1-Chloro*cyclo*hexene was prepared by the action of phosphorus pentachloride on *cyclo*hexanol-free *cyclo*hexanone (Skita and Ritter, *Ber.*, 1911, **44**, 674) and was freed from unreacted *cyclo*hexanone by treatment with semicarbazide hydrochloride; the purified liquid had b. p. 35°/13 mm. (Found: C, 61·6; H, 7·8; Cl, 30·55; reactive Cl, < 1; *I.V.*, 125. Calc. for C_6H_9Cl: C, 61·8; H, 7·8; Cl, 30·4%; *I.V.*, 218).

Monochlorodihydromyrcene was prepared by the action of chlorine on a considerable excess of dihydromyrcene (cf. Part IV), but it was difficult to separate the chlorination product from the excess hydrocarbon. The following fractions were examined: (i) b. p. 33—38°/13 mm. (Found: Cl, 8·25; reactive Cl, 7·5; *I.V.*, 315. Calc. for mixture of 40% $C_{10}H_{17}Cl$ and 60% $C_{10}H_{18}$: Cl 8·25%; *I.V.*, 329); (ii) b. p. 38—43°/13 mm. (Found: Cl, 13·3; reactive Cl, 11·8; *I.V.*, 298. Calc. for mixture of 64·5% $C_{10}H_{17}Cl$ and 35·5% $C_{10}H_{18}$: Cl, 13·3%; *I.V.*, 320); (iii) b. p. 43—46°/13 mm. (Found: C, 70·6; H, 10·0; Cl, 19·25; reactive Cl, 18·6; *I.V.*, 278. Calc. for mixture of 93·5% $C_{10}H_{17}Cl$ and 6·5% $C_{10}H_{18}$: C, 70·7; H, 10·1; Cl, 19·3%; *I.V.*, 299).

Two monochlororubbers were prepared as described in Part IV [Found: (*a*), Cl, 35·95 (34·6% substituted); reactive Cl, 24·4%. (*b*), Cl, 17·75 (all substituted); reactive Cl, 15·5%; *I.V*, 224].

Halogenation with Phenyliodochloride.—To purified rubber hydrocarbon * (5 g.) dissolved in carbon tetrachloride (300 c.c.) was added phenyliodochloride (19·2 g., 0·95 mol. per C_5H_8 unit) and the suspension was heated to boiling with stirring; a brisk reaction set in and a colourless homogeneous solution resulted. A little hydrogen chloride (0·1 g., corresponding to < 4% substitutive reaction) was evolved. The product, polyisoprene dichloride (see p. 120), isolated by precipitation with alcohol, was a white, fibrous mass (10 g.), readily soluble in most rubber solvents (Found: C, 45·4; H, 6·0; Cl, 48·1; *I.V.*, 16; intrinsic viscosity [η] in benzene, 2·125, indicating probable *M*, 127,000. Calc. for 96% additive reaction of 0·95 mol. reagent: C, 44·65; H, 5·9; Cl, 49·45%; *I.V.*, 17). Additive reaction to the extent of 98% was observed when acetone-extracted crepe rubber was brought to reaction in a similar manner but with benzoyl peroxide (4% of weight of rubber) present; when, however, quinol was substituted for the peroxide only 86% of the reagent was utilised in 30 mins. at the b. p., and 27% of the reacted phenyliodochloride chlorinated the rubber substitutively.

Action of Chlorine on Polyisoprene Dichloride.—Chlorine (2·1 g.) was passed slowly in bright light through a carbon tetrachloride solution (300 c.c.) of the dichloride (4 g.). The halogen did not react very readily and only 0·7 g. was consumed; a little hydrogen chloride (0·3 g.) was formed. The product was a white, fibrous substance (Found: Cl, 53·05; *I.V.*, 0; [η] in benzene, 1·58, indicating probable *M*, 94,000. Calc. for substitutive reaction of 0·6 g. and additive reaction of 0·1 g. chlorine: Cl, 53·0%).

Halogenations with Sulphuryl Chloride.

Method.—The reagent was diluted with an equal volume of carbon tetrachloride and run into the solution of the olefin in carbon tetrachloride at the b. p. of the latter, in the dark, and in an atmosphere of nitrogen. For the absorption system two wash-bottles containing water and a third containing aqueous sodium hydroxide (5%) were used; in the first two bottles the bulk of the sulphur dioxide and all of the hydrogen chloride formed were absorbed, and any sulphuryl chloride carried over with the gaseous reaction products was hydrolysed to hydrochloric and sulphuric acids. The third bottle trapped any sulphur dioxide swept out of the aqueous solution. The sulphur dioxide was determined iodometrically, the sulphuric acid gravimetrically, and the hydrochloric acid volumetrically (dichlorofluorescein indicator) after oxidation of sulphur dioxide with hydrogen peroxide. From the amount of hydrogen chloride formed was deducted a quantity equivalent to the sulphuric acid found to allow for sulphuryl chloride hydrolysed in accordance with the equation $SO_2Cl_2 + 2H_2O = H_2SO_4 + 2HCl$, and from the remaining hydrogen chloride was calculated the extent of substitutive chlorination in accordance with the equation $RH + SO_2Cl_2 = RCl + HCl + SO_2$.

Chlorination of cyclo*Hexene in Presence of Peroxide.*—In Kharasch and Brown's preparation (*loc. cit.*) of dichloro*cyclo*hexane, b. p. 66—68°/13 mm. (Found: C, 47·2; H, 6·7; Cl, 46·1; reactive Cl, 0·4. Calc. for $C_6H_{10}Cl_2$: C, 47·05; H, 6·6; Cl, 46·35%), the sulphur dioxide formed corresponded to utilisation of 90% of the reagent and the hydrogen chloride formed corresponded to < 5% substitutive reaction.

Chlorination of cyclo*Hexene in Presence of Antioxidant.*—Sulphuryl chloride (22·5 g.), reacting with peroxide-free *cyclo*hexene (50 g.) in the presence of quinol (0·2 g.), yielded after removal of excess *cyclo*hexene a liquid product (22·5 g.) together with sulphur dioxide (8·3 g., 78% utilisation of reagent in substitutive and additive reactions) and hydrogen chloride (0·82 g.) corresponding to 14% substitutive reaction; 5·5% of the reagent was swept out of the reaction flask. Distillation of the liquid product gave the following fractions: (i) b. p. 55—65°/13 mm. (5·9 g.); (ii) b. p. 65—70°/13 mm. (9·2 g.); (iii) b. p. < 74°/0·002 mm. (2·4 g.); (iv) b. p. 74°/0·002 mm. (3·6 g.); (v) residue (0·5 g.). Redistillation of fraction (i) gave sub-fractions (vi) b. p. 40—65°/13 mm. (3·4 g.), containing unsaturated material, and (vii) b. p. 65—68°/13 mm. (2·3 g.), saturated to iodine chloride. Fractions (ii) and (vii), total 11·7 g., were mainly dichloro*cyclo*hexane (Found: C, 47·95; H, 6·7; Cl, 45·2%). Redistillation of fractions (iii) and (iv) gave the *chloride* of 2-*chloro*cyclo*hexyl sulphite*, b. p. 74°/0·002 mm.; some sulphur dioxide was liberated before its analysis could be carried out [Found: C, 34·2; H, 4·75; Cl, 33·65; S, 13·6. $C_6H_{10}Cl_2(SO_3)_{0·9}$ requires C, 34·2; H, 4·8; Cl, 33·65; S, 13·7%]. An identical liquid resulted from the action of thionyl chloride on *cyclo*hexanol at 0° (cf. Stähler and Schirm, *loc. cit.*). The chloride reacted with water with evolution of heat, liberating 1 mol. of hydrogen chloride and less than 1 mol. of sulphur dioxide, so yielding a liquid product which gave on distillation mainly 2-chloro*cyclo*hexanol (Found: C, 53·3; H, 8·3; Cl, 26·4; OH, 12·7. Calc. for $C_6H_{11}OCl$: C, 53·55; H, 8·25; Cl, 26·35; OH, 12·6%) and a non-volatile solid residue, believed to be *bis*-(2-*chloro*cyclo*hexyl*) *sulphite*, m. p. 92° from light petroleum (Found: C, 45·95; H, 6·5; Cl, 22·65; S, 10·2. $C_{12}H_{20}O_3Cl_2S$ requires C, 45·7; H, 6·4; Cl, 22·5; S, 10·15%).

Chlorination of cyclo*Hexene in Presence of Iodine.*—Sulphuryl chloride (16·7 g.), *cyclo*hexene (30 g.), and iodine (0·2 g.) required 1½ hours at 80° for completion of reaction and yielded a liquid product (15·5 g.) together with sulphur dioxide (6·4 g., 81% utilisation of reagent) and hydrogen chloride (1·28 g., 35% substitutive reaction of reagent utilised). The liquid gave the following fractions: (i) b. p. 30—60°/13 mm. (3·6 g.), (ii) b. p. 60—68°/13 mm. (10·2 g.): the latter fraction was mainly dichloro*cyclo*hexane. Fraction (i) was united with fraction (vi) of the preceding experiment; redistillation gave a main fraction, b. p. 52—55°/13 mm. (5·0 g.), which was principally 3-chloro*cyclo*hexene (Found: C, 59·2; H, 7·6; Cl, 32·9; reactive Cl, 25·7; *I.V.*, 182. Calc. for a mixture of 82·6% C_6H_9Cl and 17·4% $C_6H_{10}Cl_2$: C, 59·2; H, 7·6; Cl, 33·2%; *I.V.*, 180).

Peroxide-catalysed Chlorination of a Chloro-substituted Rubber $(C_5H_7Cl)_n$.—A solution in carbon tetrachloride of a chlororubber [(*a*), see above (Cl, 35·95%)], obtained by the action of chlorine on rubber (4·0 g.), was treated with sulphuryl chloride (9·0 g., 1·25 mols. per C_5H_8 unit) and benzoyl peroxide (0·2 g.) at 80° in a nitrogen atmosphere in the dark. Reaction was incomplete in 2 hours and there were formed in this time sulphur dioxide (3·75 g.), corresponding to 7·7 g. of reacted sulphuryl chloride (*i.e.*, 1·02 mols. per C_5H_8 unit), and hydrogen chloride (1·11 g.), corresponding to additive reaction of 3·75 g. of reagent (0·49 mol. per C_5H_8 unit) and substitutive reaction of 4·15 g. of reagent.

* This was an oxygen-free hydrocarbon obtained by light-petroleum extraction of acetone-extracted crepe rubber from which the oxygenated fraction had been removed (Bloomfield and Farmer, *Trans. Inst. Rubber Ind.*, 1940, **16**, 69).

Peroxide-catalysed Chlorination of Dihydromyrcene.—Sulphuryl chloride (16·7 g.) and dihydromyrcene (44 c.c., 1 mol. reagent per $\frac{1}{4}$) reacting in the presence of benzoyl peroxide (0·2 g.) yielded a liquid product (38 g.) together with sulphur dioxide (7·25 g.) and hydrogen chloride (0·2 g.). The liquid gave the following fractions on distillation: (i) dihydromyrcene, b. p. 55—58°/13 mm. (14·9 g.); (ii) b. p. < 55°/0·2 mm., mainly dihydromyrcene (2·5 g.); (iii) b. p. 55—56°/0·2 mm. (14·5 g.); (iv) b. p. 56—60°/0·2 mm. (1·7 g.); (v) b. p. < 74°/0·002 mm. (1·9 g.); (vi) 74—78°/0·002 mm. (2·5 g.); residue (1·2 g.). Fraction (iii) was *dihydromyrcene dichloride* (Found: C, 57·65; H, 8·6; Cl, 33·45; reactive Cl, 5; *I.V.*, 128. $C_{10}H_{18}Cl_2$ requires C, 57·4; H, 8·7; Cl, 33·9%; *I.V.*, 122). Fraction (vi) had *I.V.* 74 and was probably mainly dihydromyrcene tetrachloride (see below).

Sulphuryl chloride (26·2 g.; 2 mols.) reacted with dihydromyrcene (13·4 g.; 1 mol.) in the presence of benzoyl peroxide (0·2 g.) to give a liquid product (27 g.) together with sulphur dioxide (11·35 g.) and hydrogen chloride (0·34 g.). Distillation of the liquid yielded *dihydromyrcene tetrachloride* (18·6 g.), b. p. 82—90°/0·002 mm. (Found: C, 43·35; H, 6·5; Cl, 50·0; *I.V.*, < 2. $C_{10}H_{18}Cl_4$ requires C, 42·9; H, 6·5; Cl, 50·6%), together with a little liquid (0·8 g.) of lower b. p. and some residue (3·8 g.). Part of the dihydromyrcene tetrachloride crystallised on standing; the crystals (from methanol) had m. p. 50° (Found: C, 42·9; H, 6·55; Cl, 50·7%).

Peroxide-catalysed Chlorination of Rubber.—The rubber (4 g.) (see footnote, p. 119) was dissolved in carbon tetrachloride (250 c.c.) under conditions precluding access of air, and allowed to react at 80° with sulphuryl chloride (7·8 g.) in the presence of benzoyl peroxide (0·1 g.); there were formed sulphur dioxide (3·5 g.) and hydrogen chloride (0·1 g.). The reaction product (8·0 g.), isolated by precipitation with alcohol, was indistinguishable from the *polyisoprene dichloride* described above (Found: C, 43·1; H, 5·7; Cl, 51·25; reactive Cl, 3; *I.V.*, 14; $[\eta]$ in benzene, 2·015, indicating probable *M*, 120,000. $C_5H_8Cl_2$ requires C, 43·1; H, 5·75; Cl, 51·15%; *I.V.*, 0). This product was stable in air and at 80°.

From crepe rubber (10 g.) and sulphuryl chloride (10 g.) there were formed sulphur dioxide (4·4 g.), hydrogen chloride (2·2 g.), and a rubber-like product (12 g.), which was unstable on exposure to air or on heating (Found: Cl, 23·0; reactive Cl, 16·5. Calc. for 90% substitutive and 10% additive reaction: substituted Cl, 18·5; total Cl, 23·5%). From acetone-extracted crepe rubber (5 g.) and sulphuryl chloride (5 g.) there was similarly obtained 0·6 g. of hydrogen chloride, corresponding to 45% substitutive reaction.

Halogenation with N-Bromosuccinimide.

Bromination of Dihydromyrcene.—*N*-Bromosuccinimide (18 g., 1 atom Br per $C_{10}H_{18}$) and dihydromyrcene (17·7 c.c.) in carbon tetrachloride (100 c.c.) were kept at 77° in an atmosphere of nitrogen; no hydrogen bromide was liberated. Distillation of the product, after separation of succinimide (9·9 g.), yielded a liquid fraction, b. p. 54°/0·1 mm., together with some unreacted dihydromyrcene and considerable residue. The liquid was *monobromodihydromyrcene* (Found: C, 55·2; H, 7·9; Br, 36·5; reactive Br, 36·2; *I.V.*, 226. $C_{10}H_{17}Br$ requires C, 55·3; H, 7·9; Br, 36·8%; *I.V.*, 234).

Bromination of Rubber.—Reaction between *N*-bromosuccinimide (6·6 g., 1 atom Br per two C_5H_8 units) and acetone-extracted crepe rubber (5 g.) in carbon tetrachloride (300 c.c.) was complete in 30 mins., giving a reddish-brown solution; no hydrogen bromide was liberated. As soon as the reddish-brown, rubber-like product (7·8 g.) was freed from solvent it could not be redissolved; consequently the reactive bromine and the iodine value could not be directly determined. The preparation was therefore repeated in benzene solution and 10 c.c. portions of the solution were taken for these determinations. The bromo-rubber content of the solution was also determined by evaporation in a vacuum of a 10 c.c. portion, the residue being subsequently thoroughly extracted with methanol (Found: C, 55·5; H, 7·1; Br, 37·4; reactive Br, 35; *I.V.*, 155. $C_{10}H_{15}Br$ requires C, 55·8; H, 7·0; Br, 37·2%; *I.V.*, 236).

The Action of Bromine on Rubber.—A solution of sol rubber (5·0 g.) in chloroform (350 c.c.) was cooled to between − 30° and − 40°, and a solution of bromine (11·8 g., 1·0 mol. per C_5H_8 unit) and iodine (0·1 g.) in carbon tetrachloride (100 c.c.) was added in the dark, with shaking, in an atmosphere of nitrogen. No hydrogen bromide was evolved during the addition or on bringing the gelled solution to room temperature. The insoluble, pale brown, resinous product (16·5 g. Found: Br, 69·0. Calc. for $C_5H_8Br_2$: Br, 70·1%) did not evolve hydrogen bromide at temperatues up to 80° although it darkened considerably.

Hydrogen bromide was formed in considerable quantity (0·6—0·8 g.) when rubber (5 g.) in carbon tetrachloride or carbon disulphide was treated at 0° with bromine (5·9 g., 0·5 mol. per C_5H_8 unit) in the same solvent, under various conditions permitting access or exclusion of light, moisture, and oxygen. When either chloroform or carbon tetrachloride containing alcohol (1%) was used as solvent no hydrogen bromide was liberated. The most rapid bromination took place in chloroform; moreover, there was no separation of the brominated product even when a full molecular proportion of bromine per C_5H_8 unit was added. No change in *I.V.* and no liberation of hydrogen bromide were observed on heating solutions of partly brominated rubbers (0·5—0·8 mol. of bromine per C_5H_8 unit) at 80° for an hour.

For a rapid estimation of rubber hydrocarbon, the sample (acetone-extracted crepe rubber, 0·1 g.) was dissolved in chloroform (50 c.c.) and cooled to 0°. Approximately twice the theoretical quantity of bromine was added in chloroform solution of known concentration, and the excess was estimated by treatment with potassium iodide solution followed by volumetric estimation of the liberated iodine (Found: *I.V.*, by bromine addition, 357; *I.V.*, by Kemp's modification of the Wijs procedure, 360).

Corrigendum.—The fraction, b. p. 56—60°/0·01 mm., obtained by the chlorination of 1-methyl*cyclo*hexene (Part IV) was mainly trichloromethyl*cyclo*hexane (Found: Cl, 49·9. Calc for $C_7H_{11}Cl_3$: Cl, 50·2%) and not methyl*cyclo*hexene dichloride as formerly assumed.

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44. *Rubber, Polyisoprenes, and Allied Compounds. Part VII. Action of Nitric Oxide thereon.*

By George F. Bloomfield and (in part) G. A. Jeffrey.

The reaction of nitric oxide with the olefins *cyclo*hexene, 1-methyl*cyclo*hexene, dihydromyrcene, and rubber presents characteristics of a free-radical, chain reaction. In the products the molecular ratio of combined oxygen to nitrogen is considerably in excess of 1 : 1, the nitrogen atom being generally directly linked to carbon. In many instances definite nitro-compounds have been isolated, and a considerable part of the attack appears to

proceed at the ethylenic carbon atoms, either by substitution or addition of NO_2 and N_2O_3 groups. The precise reaction mechanism is obscure.

ALTHOUGH the reactions of nitrogen dioxide, dinitrogen trioxide, and nitrosyl chloride with olefins have been studied extensively, the action of nitric oxide has received but little attention and it has in fact been stated (Sidgwick, " The Organic Chemistry of Nitrogen," **1937**, p. 213) that it does not combine with a normal ethylenic linkage. Nitric oxide is, however, of well-established utility in the study of free-radical reactions, which it can promote, retard, or inhibit in virtue of its property of starting reaction chains, or stopping them by combination with other free radicals.

General Characteristics of the Reaction of Nitric Oxide with Olefins.—Characteristics of a free-radical mechanism were exhibited. For instance, when a solution of rubber, dihydromyrcene, 1-methyl*cyclo*hexene, or *cyclo*hexene was shaken in contact with nitric oxide there was generally an induction period of 15—30 minutes, depending on the intensity of the prevailing light, before any sign of reaction became evident. Then the solution acquired a pronounced green colour, absorption of nitric oxide commenced, and some heat was evolved. The induction period was not confined to the initial starting of the reaction, for if the reaction was stopped by removing the nitric oxide from the system and then, after a short interval, nitric oxide was readmitted, an induction period was again observed before reaction recommenced. Under the conditions employed, the reaction ceased owing to admixture by nitrogen produced in the reaction. When provision was made for removing the nitrogen, no difficulty was experienced in carrying the reaction as far as was desired, and it became obvious that absorption of nitric oxide could proceed far beyond one molecular proportion per double bond, and that the volume of nitrogen formed was generally between a third and a quarter of the volume of nitric oxide which had been absorbed at any given stage of the reaction. The formation of nitrogen in reactions of nitric oxide with free radicals (but not with olefins) has been reported by Nauta and Mulder (*Rec. Trav. chim.*, **1939**, **58**, 1070) and by Sonneborn and Wiselogle (*J. Amer. Chem. Soc.*, **1942**, **64**, 860), who attributed its formation to decomposition of an intermediate hyponitrite.

Obviously the reaction of nitric oxide with olefins does not proceed by any simple attachment of nitric oxide itself to the unsaturated molecule, and it is not surprising that a variety of products was isolated containing nitrogen in various states of combination with oxygen.

Reaction with Rubber.—Gorgas's observation (*Ber.*, **1930**, **63**, 2700) that an insoluble nitrogenous product was precipitated by the action of nitric oxide on a rubber solution has been confirmed. This occurred at a stage represented by the absorption of approximately 1 mol. of nitric oxide per C_5H_8 unit, and the composition of the product corresponded with the introduction into half of the available C_5H_8 units of groups containing nitrogen and oxygen in the ratio 1 : 2 to 1 : 2·7, varying from one preparation to another. At a somewhat earlier stage the product could be separated into two components of approximate compositions $C_{10}H_{15}O_3N$ and $C_{10}H_{15}O_4N$. In the early stages of reaction there was considerable reduction of molecular size, by an obscure mechanism which required the absorption of a proportion of nitric oxide appreciably greater than the proportion of oxygen required to bring about a comparable reduction in molecular size (Farmer and Sundralingam, J., **1943**, 125).

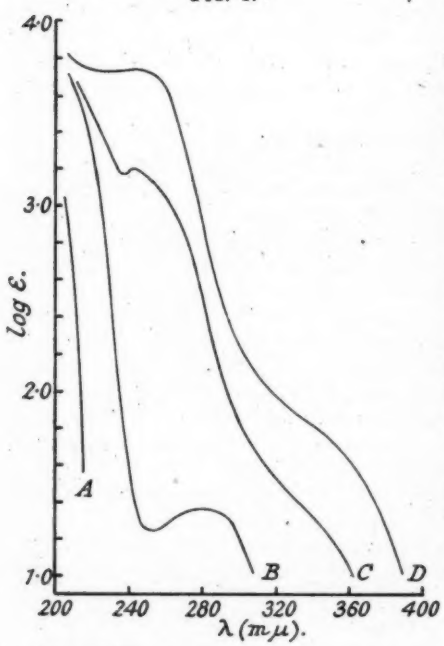
Reaction with Simpler Olefins allied to Rubber.—Dihydromyrcene and 1-methyl*cyclo*hexene yielded products which appeared to contain substituent nitro-groups, together with substances of rather lower oxygen : nitrogen ratio. In the formation of the former products the unsaturation was considerably affected, being much lower than that calculated for simple nitro-substituted olefins.

*cyclo*Hexene yielded the following products : (1) the already known crystalline *cyclo*hexene *pseudo*-nitrosite * (Baeyer, *Annalen*, **1894**, **278**, 110; Wieland, *ibid.*, **1921**, **424**, 71), (ii) a mixture of isomeric nitro*cyclo*hexenes containing a considerable proportion of 1-nitro*cyclo*hexene, and (iii) an unstable, non-distillable, viscous oil constituting the major product. Partial separation of the isomeric nitro*cyclo*hexenes yielded a fairly pure sample of the 1-nitro-isomer but the other isomer, in all probability 3-nitro*cyclo*hexene, could not be isolated in a pure state since it underwent considerable decomposition in the presence of alkali (cf. the instability of α-methylene-substituted halogen; preceding paper). The constitution of the 1-nitro*cyclo*hexene was established by oxidation to adipic acid and by reduction to *cyclo*hexanoneoxime, the latter reaction probably proceeding through the intermediate *cyclo*hexenylhydroxylamine (cf. the reduction of nitro*cyclo*hexane to *cyclo*hexylhydroxylamine), or possibly by direct 1 : 4-addition of hydrogen to the C:C·N:O system. As was expected from the presence on the ethylenic carbon atom of a strongly polar group, capable of forming a conjugated system with the ethylenic linkage, addition of iodine chloride to the $>C=C<$ bond was almost completely inhibited, but the additive capacity for hydrogen established the presence of the ethylenic linkage. Spectrographic examination by Dr. H. P. Koch, for which the authors' thanks are due, has confirmed the presence of considerable conjugation in the 1-nitro*cyclo*hexene component of the mixture (Fig. 1). The other nitro*cyclo*hexene which was present exhibited a much more satisfactory additive capacity for iodine chloride. The constitution of the major non-volatile reaction product has not been established; it was a unimolecular substance exhibiting no additive capacity for iodine chloride, with groups containing oxygen and nitrogen in a ratio slightly in excess of 2 : 1 added or substituted at the original ethylenic linkage of the *cyclo*hexene; treatment with alkali gave a crystalline product of higher nitrogen content than the original oil, suggesting the presence of stable carbon–nitrogen linkages.

* The bimolecular structure proposed by Wieland has been confirmed by *X*-ray examination (p. 123).

The principal characteristics of the reaction under consideration are therefore: (1) Various products are formed; all contain nitrogen directly linked to carbon, and the nitrogen is combined with oxygen in the proportion 1 : 2, 2 : 3, or 1 : 3; several of the products are identical with those known to be formed by the action of higher oxides of nitrogen on the corresponding olefin. (2) At least 1 mol. of nitrogen is formed for every 4 mols. of nitric oxide reacting. (3) When substitutive reaction is taken into account, the H : C ratio is substantially preserved. (4) The ethylenic carbon atoms are extensively involved in substitutive and additive reactions. (5) The reaction is inhibited by alcohol or acetic acid.

FIG. 1.



A.—*cyclo*Hexene.
B.—Nitro*cyclo*hexane.
C.—Mixture of isomeric nitro*cyclo*hexenes.
D.—1-Nitro*cyclo*hexene (mainly).

Since most of the reaction products are precisely those obtained by the action of higher oxides of nitrogen or of nitrous acid, it is likely that reaction proceeds by conversion of the nitric oxide into a higher state of oxidation, probably by a free-radical chain mechanism involving the hydrocarbon. The attack at the ethylenic carbon atoms may be closely related to the preferential attack of free halogen radicals at these carbon atoms (preceding paper). Any such reaction must occur in the liquid phase, since brown fumes in the gas phase were not observed; the presence of nitrous acid or, more probably, dinitrogen trioxide in the liquid phase was, however, detected by Sonneborn and Wiselogle's procedure (*loc. cit.*) during the course of the reaction. If nitrous acid itself is formed, it must become involved in a course of reaction other than the usual formation of ψ-nitroles with those secondary nitro-groups already present. The formation of some of the reaction products is satisfied by overall reactions of the type represented by the equations

(*a*) $RH + 4NO = RNO_2 + N_2 + HNO_2$ or
$2RH + 8NO = 2RNO_2 + 2N_2 + N_2O_3 + H_2O$

(*b*) $>C{:}C< + N_2O_3 = >C(NO)\cdot\overset{|}{C}(NO_2)$

(*c*) $2RH + 10NO = 2RNO_3 + 3N_2 + 2HNO_2$ or
$2RH + 10NO = 2RNO_3 + 3N_2 + N_2O_3 + H_2O$.

EXPERIMENTAL.

(Microanalyses were carried out by Dr. W. T. Chambers and Miss H. Rhodes.)

Reactions were conducted either in a glass globe or in a small flask fitted with a sintered-glass distributor through which gas could be passed, first from reservoir *A* into reservoir *B* (Fig. 2), and then back into *A* by manipulation of the

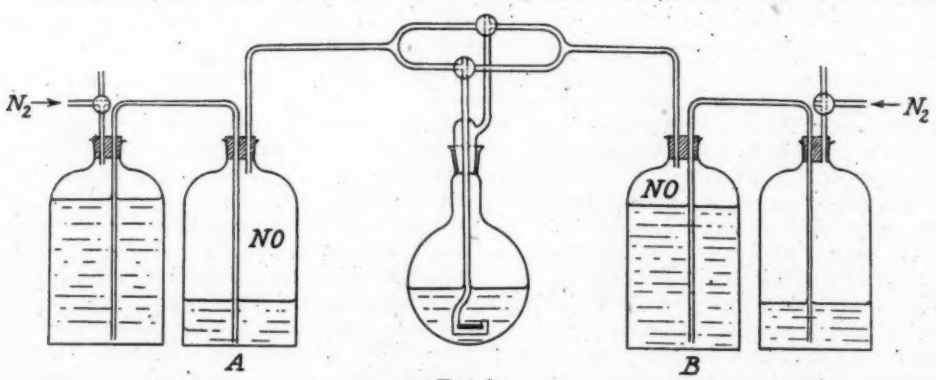


FIG. 2.

stopcocks and application of nitrogen pressure to the reservoirs. The apparatus was first swept out with purified nitrogen, then evacuated until the solvent had boiled vigorously for a few minutes under the reduced pressure, refilled with nitrogen, re-evacuated, and finally filled with nitric oxide obtained from sodium nitrite, potassium ferrocyanide, and acetic acid. The gas remaining at the conclusion of an experiment was displaced into a measuring system and, after removal of any nitric oxide with aqueous potassium permanganate, the volume of residual nitrogen was measured.

Experiments with Rubber.—The hydrocarbon (sol rubber, 5 g.) was dissolved in carbon tetrachloride (300 c.c.); reaction required 30—120 mins. The results are in the table.

Experiments with Dihydromyrcene and 1-*Methyl*cyclo*hexene.*—Dihydromyrcene (15·6 g.) in carbon tetrachloride (150 c.c.) was shaken with nitric oxide (1888 c.c., N.T.P.) in the glass globe during 8 hours in diffused sunlight. The residual gas (588 c.c.) contained a little nitric oxide (38 c.c.), whence the nitric oxide consumed and the nitrogen formed were equivalent to 0·73 mol. and 0·22 mol. respectively per mol. of dihydromyrcene. A little yellow resin was precipitated. The yellow supernatant solution yielded on distillation unreacted dihydromyrcene (10·8 g.), a liquid fraction, b. p. 66—70°/0·001 mm. (0·6 g.), and considerable residue (4·1 g. Found: C, 55·55; H, 8·5; N, 11·6%; *I.V.*,

Reaction of Nitric Oxide with Rubber.

NO consumed, mols. per C_5H_8 unit.	N_2 formed, mols. per mol. NO.	Analysis of product, %. C.	H.	N.	O.	*I.V.*	Solubility of product.
0·13	—	84·2	11·3	—	—	—	Soluble
0·15	0·28	83·9	11·3	1·65	3·2	—	,, *
0·19	0·23	83·15	11·1	—	—	—	,,
0·48	0·25	76·0	10·15	4·2	9·65	262	,, †
0·94	0·24 ‡	—	—	—	—	—	,,
0·95	0·29	68·7	9·05	6·0	16·25	220	Partly insol.
ca. 1·0	—	63·25	8·45	7·85	20·3	—	Insol.
ca. 0·9	—	68·0	8·9	6·95	16·15 §	—	Insol. part, 74% of product
		60·7	7·85	6·85	24·6 ‖	—	Soluble part, 26% of product
1·35	0·29 ‡	—	—	—	—	—	Insol.

* Intrinsic viscosity 0·74 in benzene + 15% methanol; mol. wt. 74,000 (original mol. wt. 238,000).
† Intrinsic viscosity 0·57 in benzene; mol. wt. 33,000 (original mol. wt. 220,000).
‡ In these experiments the absence of carbon dioxide in the residual gas was demonstrated by passage of the latter through a weighed CO_2-absorption tube.
§ Empirical formula $C_{10}H_{15\cdot6}(NO_2)_{0\cdot9}$. ‖ Empirical formula $C_{10}H_{15\cdot4}NO_2$.

79, corresponding to $C_{10}H_{16}O_{2\cdot2}N_{1\cdot2}$). The liquid fraction was probably a *nitrodihydromyrcene* [Found: C, 65·6; H, 9·4; N, 7·7; *I.V.*, 156. $C_{10}H_{17}O_2N$ requires C, 65·5; H, 9·35; N, 7·65%; *I.V.*, 277 ($\frac{2}{2}$), 139 ($\frac{2}{1}$)].

1-Methyl*cyclo*hexene similarly yielded a liquid product, b. p. 50°/0·01 mm., probably a *nitromethyl*cyclo*hexene* (Found: C, 59·3; H, 8·0; N, 10·0; *I.V.*, 73. $C_7H_{11}O_2N$ requires C, 59·55; H, 7·85; N, 9·9%; *I.V.*, 180), and some viscous residue.

Reaction with cyclo*Hexene*.—Nitric oxide equivalent to 1·6 mols. per mol. of *cyclo*hexene was consumed during 15 hours in a dull light, with formation of 0·44 mol. of nitrogen; a white, crystalline solid separated continuously from the commencement of the reaction. This (2·44 g.) was filtered off and the filtrate yielded on distillation a pale yellow liquid, b. p. 33—46°/0·01 mm. (*ca.* 6 g.), and considerable residue (14·4 g.).

Crystalline solid. This was *cyclo*hexene *ψ*-nitrosite, m. p. 153° (decomp.) from benzene, mixed m. p. with authentic specimen 153° (decomp.) (Found: C, 45·55; H, 6·35; N, 17·5; *I.V.*, 0. Calc. for $C_6H_{10}N_2O_3$: C, 45·55; H, 6·35; N, 17·75%); recrystallisation from chloroform–alcohol separated it into triclinic needles, m. p. 153° (decomp.), $d_4^{20°}$ 1·389, and monoclinic prisms, m. p. 153° (decomp.), $d_4^{20°}$ 1·378.

Note on crystal structure of cyclo*hexene nitrosites* (by G. A. Jeffrey). The triclinic needles had cell dimensions $a = 7·19$ A., $b = 10·20$ A., $c = 5·15$ A., $\alpha = 90°$, $\gamma = 98°$, $\beta = 104·5°$, whence the calculated density for $2(C_6H_{10}N_2O_3)$ was 1·35. The space group may be $P1$ with an asymmetric dimeric molecule, or $P\bar{1}$ with two monomers or one centrosymmetric dimer. These dimensions, particularly the short c axis, impose certain limitations on the choice of possible configurations for this compound. About 3·3 A. being allowed as the nearest approach of atoms in adjacent molecules between which there are only ordinary van der Waals forces, it follows that the width of the molecules along any line parallel to the c axis must not exceed about 2·2 A. For the monomeric nitrosite there are a number of configurations to consider depending upon the positions of the NO_2 and NOH groups and the shape of the ring. Two such arrangements, one with a Sachse boat-shaped ring and the other with the chair-shaped ring, would give the necessary flat molecules, but neither of these could be packed into the unit cell without a much closer association than 3 A. between atoms of adjacent molecules. The triclinic form must therefore be dimeric.

The monoclinic prisms had cell dimensions $a = 11·44$ A., $b = 12·28$ A., $c = 11·06$ A., $\beta = 101° 21'$, whence the density calculated for 4 dimeric or 8 monomeric molecules in the cell was 1·36. The space-group was $P2_1/c$. Although the cell dimensions give little guide to the molecular shape, there is scarcely sufficient room to accommodate eight monomeric molecules and four dimers seems the more likely.

Consideration of the configurations for the dimeric molecules is complicated by uncertainty of the true nature of the associating link (cf. Sidgwick, *op. cit.*, p. 214). For the triclinic form, only a molecule with the C–N (nitro) bonds approximately in the plane of the ring is consistent with the short axis, and for the monoclinic prisms a stereoisomeric arrangement with the nitro-group projecting out of the plane is possible.

Liquid product. This appeared to be a mixture of isomeric nitro*cyclo*hexenes (Found: C, 56·6; H, 7·15; N, 11·3; *I.V.*, 75. Calc. for $C_6H_9O_2N$: C, 56·7; H, 7·15; N, 11·0%; *I.V.*, 200), the presence of the nitro-group being indicated by the following facts: (1) Close resemblance to authentic nitro*cyclo*hexenes prepared by two different methods (see below). (2) The blue colour characterising a secondary nitro-group was observed on treatment with nitrous acid. (3) The active hydrogen content (*ca.* 0·1%), which probably arose from partial isomerisation of the nitro-group, was much too low to permit of the presence of a hydroxyl group. (4) No derivatives characterising a carbonyl or a hydroxyl group could be obtained. (5) cyclo*Hexyl nitrite* (Found: C, 56·2; H, 8·8; N, 10·8. $C_6H_{11}O_2N$ requires C, 55·75; H, 8·6; N, 10·8%), prepared by the action of nitrous acid on *cyclo*hexanol, had a considerably lower b. p. (<30°/13 mm., 41°/20 mm.) than the liquid under consideration. (6) Reduction with zinc dust in acetic acid gave a 30% yield of *cyclo*hexanone-oxime, m. p. 75—79°, mixed m. p. with authentic specimen (m. p. 84—85°) 79—81° (Found: C, 63·1; H, 9·65; N, 12·3. Calc. for $C_6H_{11}ON$: C, 63·2; H, 9·7; N, 12·3%). Reduction of nitro*cyclo*hexane under the same conditions yielded cyclo*hexylhydroxylamine*, m. p. 137° (Found: C, 62·6; H, 11·4; N, 12·1. $C_6H_{13}ON$ requires C, 62·55; H, 11·4; N, 12·15%), which was sparingly soluble in water (solution feebly alkaline). (7) Hydrogen uptake was 7 atoms per mol. with Adams's catalyst, 8 atoms per mol. with Raney nickel. (8) The ultra-violet absorption spectrum (curve *C*, Fig. 1) established the presence of considerable conjugation. (9) To 3·4 g. of the liquid, stirred with 2N-sodium hydroxide (14 c.c.), was added a 3% solution of potassium permanganate (315 c.c.) at 0—20°; the yield (1·3 g.) of adipic acid, m. p. 151°, mixed m. p. 151° (Found: C, 49·5; H. 6·95; equiv., 73. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 6·9%; equiv., 73), established the presence of at least 40% of 1-nitro*cyclo*hexene in the sample. (10) 1-Nitro*cyclo*hexene was partly separated from the accompanying isomer by shaking with cold N-sodium hydroxide, in which 1-nitro*cyclo*hexene was known to be insoluble, and then extracted with ether. The alkali-insoluble portion had b. p. 35—36°/0·01 mm., and 1·0 g. gave 0·8 g. of adipic acid (equivalent to 0·7 g. of nitro*cyclo*hexene) on oxidation as above; (Found: C. 56·65; H, 7·3; N, 10·7%; *I.V.*, 23). (For ultra-violet absorption spectrum see curve *D*, Fig. 1.) The alkali-soluble portion, b. p. 30—42°/0·01 mm., had undergone partial hydrolysis * [Found: C, 61·2; H, 7·7; N, 8·5; *I.V.*, 119. Calc. for mixture of 75% $C_6H_9{\cdot}NO_2$ and 25% $C_6H_9{\cdot}OH$ (?): C, 60·9; H, 7·7; N, 8·5%; *I.V.*, 215].

* A high order of reactivity of groups substituted at the 3-position of *cyclo*hexene has already been observed in halogen-substitution products (preceding paper).

Examination of other specimens of nitrocyclohexene. 1-Nitro*cyclo*hexene, b. p. 45—50°/0·1 mm. (Found : C, 56·0; H, 7·53; N, 10·8%; *I.V.*, 29), prepared according to Wieland (*loc. cit.*), was insoluble in N-sodium hydroxide; 1·9 g. gave 1·1 g. of adipic acid on oxidation, and the hydrogen uptake (Adams's catalyst) was 7 atoms per mol. 3(?)-Nitro*cyclo*hexene, b. p. 34°/0·01 mm. (Found: C, 56·25; H, 7·1; N, 10·9%; *I.V.*, 155), prepared by the action of alkali on *cyclo*hexene ψ-nitrosite (Wieland) was soluble (with partial hydrolysis *) in N-sodium hydroxide; 0·8 g. gave 0·15 g. of adipic acid, corresponding to the presence of 16% 1-nitro*cyclo*hexene, and the hydrogen uptake (Adams's catalyst) was 7·5 atoms per mol.

Residue. This slowly decomposed at room temperature and could not be distilled without severe decomposition. An effective separation from *cyclo*hexene ψ-nitrosite was achieved by dissolution in methanol at 0°, in which the nitrosite was insoluble; removal of the alcohol gave a brown viscous oil. The products of four separate reactions were remarkably constant in composition [Found : C, 44·6±0·5; H, 6·1±0·1; N, 13·9±0·1%; *I.V.*, 4; *M* (f. p. depression in benzene), 164], which corresponded to the formula $C_6H_{10}O_{3\cdot6}N_{1\cdot6}$. Oxidation of 4·6 g. with alkaline permanganate (3%, 270 c.c.) proceeded only slowly and yielded an unidentified neutral oil (0·55 g.) and adipic acid (1·7 g.). Oil (5·4 g.) in alcoholic potassium hydroxide (100 c.c., 0·82N) at the b. p. for 15 mins. yielded a large and a small portion respectively soluble and insoluble in alkali. Distillation of the former yielded a little impure nitro*cyclo*hexene, b. p. 40—47°/0·1 mm. (Found : C, 57·1; H, 7·4; N, 10·6. Calc. for mixture of 96·75% $C_6H_9{\cdot}NO_2$ and 3·25% $C_6H_9{\cdot}OH$: C, 57·15; H, 7·25; N, 10·5%), and a considerable residue from which an unidentified crystalline *solid* separated, m. p. 107—108° from benzene (Found : C, 46·0; H, 5·15; N, 17·7. $C_6H_8O_2N_2$ requires C, 46·1; H, 5·15; N, 17·95%).

The reaction of nitric oxide with *cyclo*hexene did not proceed in alcoholic solution, or in a medium containing acetic acid. Nitric oxide did not react with nitro*cyclo*hexene in carbon tetrachloride.

This paper forms part of a programme of fundamental research undertaken by the Board of the British Rubber Producers' Research Association. The author expresses his thanks to Dr. E. H. Farmer for his advice and criticism, and to Dr. G. Gee for molecular-weight determinations.

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45. *The Action of Phosphorus Pentasulphide on Barbituric Acids.*

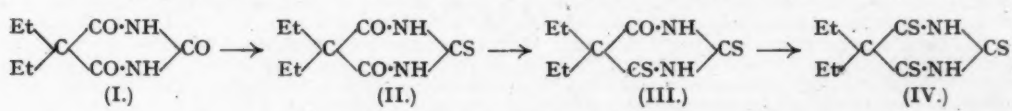
By H. C. Carrington.

When barbituric acids containing two hydrocarbon residues in the 5-position react with phosphorus pentasulphide, one, two or three of the oxygen atoms of the barbituric acid ring may be replaced by sulphur according to the conditions of the reaction and the nature of the substituents.

Thiobarbituric acids are generally prepared by condensation of substituted malonic esters with thiourea, leading to 5-substituted 2-thiobarbituric acids. Until recently, no substituted barbituric acids were known in which more than one of the oxygen atoms were replaced by sulphur, although the preparation of 2 : 4 : 6-trithiobarbituric acid by the action of potassium hydrosulphide on 2 : 4 : 6-trichloropyrimidine had been described (Büttner, *Ber.*, 1903, **36**, 2234). The conversion of amides into thioamides by heating with phosphorus pentasulphide is well known, and Kindler (*Annalen*, 1923, **431**, 187) has described an improved technique for this reaction. A study of the direct sulphurisation of substituted barbituric acids by the action of phosphorus pentasulphide has now been made. While the results of this work were being prepared for publication, an account appeared (Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090) of the conversion of two substituted barbituric acids into the corresponding trithio-compounds by heating under reflux with phosphorus trisulphide in tetralin solution. This method is closely related to that here described, and the two products, 5-phenyl-5-ethyl-2 : 4 : 6-trithiobarbituric acid and 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid, are among the compounds described in the present communication.

A series of barbituric acids, mostly well known hypnotics, carrying hydrocarbon substituents in the 5-position, has been used, and according to the nature of the substituents and the conditions of the reaction, one, two or three oxygen atoms may be replaced by sulphur. Simple fusion of the barbituric acid with phosphorus pentasulphide may lead to the formation of thiobarbituric acids, but the yields are extremely low, and the conditions used by Kindler in the preparation of thioamides give much better results. He carried out the reaction in the presence of an alkali polysulphide, and in an indifferent liquid medium. In the case of the barbituric acids this medium may be varied considerably; hydrocarbons and chlorohydrocarbons of different types, and also ethers, have been used.

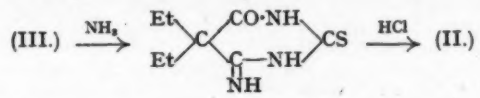
The sulphurisation of 5 : 5-diethylbarbituric acid (I) has been studied in some detail. In boiling toluene the product is a mixture of a 5 : 5-diethyldithiobarbituric acid and 5 : 5-diethyl-2-thiobarbituric acid (II), identical with that synthesised from ethyl diethylmalonate and thiourea. In boiling xylene a mixture of the same 5 : 5-diethyldithiobarbituric acid with 5 : 5-*diethyl*-2 : 4 : 6-*trithiobarbituric acid* (IV) is obtained. This suggests that the sulphurisation proceeds by stages, the " urea " oxygen atom being replaced first :



(I.) (II.) (III.) (IV.)

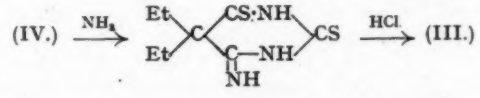
The formulation of the dithio-compound as 5 : 5-*diethyl*-2 : 4-*dithiobarbituric acid* (III) is supported by the following evidence. 5 : 5-Diethyl-2 : 4-dithiobarbituric acid can be converted into 5 : 5-diethyl-2-thiobarbituric

acid by reaction with ammonia to give 4-imino-5 : 5-diethyl-2-thiobarbituric acid, followed by hydrolysis with dilute acid :



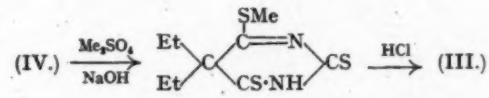
Furthermore, the sulphurisation of 5 : 5-diethyl-2-thiobarbituric acid synthesised from ethyl diethylmalonate and thiourea gives a mixture of the same 5 : 5-diethyl-2 : 4-dithiobarbituric acid and 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid as that obtained from 5 : 5-diethylbarbituric acid itself.

5 : 5-Diethyl-2 : 4 : 6-trithiobarbituric acid with aqueous ammonia affords 6-*imino*-5 : 5-*diethyl*-2 : 4-*dithiobarbituric acid*, which is readily converted by acid hydrolysis into 5 : 5-diethyl-2 : 4-dithiobarbituric acid :



The insolubility of the imino-compound in aqueous ammonia may account for the fact that only one of the two thioamide sulphur atoms in the trithio-compound is replaced by an imino-group.

Treatment of 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid in aqueous sodium hydroxide with methyl sulphate affords the 6-*methylthio*-derivative, which is readily hydrolysed by dilute acid to 5 : 5-diethyl-2 : 4-dithiobarbituric acid :



Barbituric acids with two primary alkyl groups in the 5-position sulphurise readily, and both di- and tri-thio-compounds can usually be obtained. The same holds true with a phenyl group in the 5-position. If, however, one of the substituents is a secondary alkyl group, the barbituric acid is more resistant to sulphurisation, and under the usual reaction conditions only monothio-compounds are generally formed. As would be expected, these are the 2-thio-compounds.

Experimental.

Preparation of the Substituted Barbituric Acids.—All the acids used have been previously described. Many of them are well-known hypnotics and are readily available. The others were synthesised from the corresponding substituted malonic or cyanoacetic esters by methods described in the literature.

Sulphurisation of 5 : 5-Diethylbarbituric Acid.—(a) *Action of phosphorus pentasulphide and liver of sulphur in boiling xylene.* A mixture of 5 : 5-diethylbarbituric acid (20 g.), phosphorus pentasulphide (20 g.), and liver of sulphur (30 g.) was stirred with xylene (350 c.c.) and refluxed for 16 hours. The hot liquid was filtered and, after cooling, the orange crystalline precipitate was separated. Fractional crystallisation from methyl alcohol or benzene gave 5 : 5-*diethyl*-2 : 4-*dithiobarbituric acid* (5 g.), bright yellow plates, m. p. 205—206°, readily soluble in methyl alcohol, sparingly soluble in benzene (Found : C, 44·7; H, 5·9; N, 12·9; S, 29·7. $C_8H_{12}ON_2S_2$ requires C, 44·5; H, 5·6; N, 13·0 : S, 29·6%), and 5 : 5-*diethyl*-2 : 4 : 6-*trithiobarbituric acid* (10 g.), deep orange-red needles, m. p. 192—193°, sparingly soluble in methyl alcohol, fairly readily soluble in benzene (Found : C, 41·75; H, 5·25; N, 12·15; S, 40·9. $C_8H_{12}N_2S_3$ requires C, 41·4; H, 5·2; N, 12·1; S, 41·4%). Both compounds darken with rise of temperature, and revert to their original light colour on cooling, without apparent change in crystalline state. They are very sparingly soluble in water, readily soluble in alkali, and reprecipitated by acid.

(b) *Variation in the conditions of sulphurisation.* In boiling benzene no reaction took place. In boiling toluene a mixture was obtained of 5 : 5-diethyl-2-thiobarbituric acid (m. p. 173°, identical with material synthesised from ethyl diethylmalonate and thiourea) and the 5 : 5-diethyl-2 : 4-dithiobarbituric acid described above. When 5 : 5-diethylbarbituric acid was fused with phosphorus pentasulphide at 200°, there was a small yield of a crystalline sublimate which was a mixture of the di- and the tri-thio-compound, but no identifiable compound could be isolated from the main mass of the melt.

Sulphurisation of 5 : 5-Diethyl-2-thiobarbituric Acid.—5 : 5-Diethyl-2-thiobarbituric acid (5 g.) was stirred and refluxed for 16 hours with phosphorus pentasulphide (5 g.), liver of sulphur (8 g.), and xylene (70 c.c.). After filtration and cooling, the product which crystallised was a mixture of 5 : 5-diethyl-2 : 4-dithiobarbituric acid (m. p. 205—206°) and 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid (m. p. 192—193°).

6-*Imino*-5 : 5-*diethyl*-2 : 4-*dithiobarbituric Acid.*—A solution of 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid (4 g.) in aqueous ammonia (*d* 0·88, 40 c.c.) was warmed on the steam-bath for ½ hour; hydrogen sulphide was evolved and a bright yellow solid separated. After cooling, this was collected and recrystallised from methyl alcohol. It decomposed at about 230° (2·3 g.) (Found : N, 19·4; S, 29·5. $C_8H_{13}N_3S_2$ requires N, 19·55; S, 29·8%). The *imino*-compound was hydrolysed quantitatively to 5 : 5-diethyl-2 : 4-dithiobarbituric acid by warming for 20 minutes with 4% hydrochloric acid.

6-*Methylthio*-5 : 5-*diethyl*-2 : 4-*dithiobarbituric Acid.*—To a solution of 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid (10 g.) in 4% aqueous sodium hydroxide (200 c.c.), methyl sulphate (6 g.) was added during 15 minutes. The mixture was stirred at 20° for 2 hours. A small quantity of dark insoluble matter was separated, and hydrochloric acid (36%) added with cooling until the mixture was just acid to Congo-red. A dark red oil separated, which rapidly solidified. After being stirred with 5% aqueous sodium carbonate at 45° to remove unchanged 5 : 5-diethyl-2 : 4 : 6-trithiobarbituric acid, the product was recrystallised from aqueous methyl alcohol, forming a dark red solid (3·5 g.), m. p. 130° (Found : N, 11·9; S, 39·2. $C_9H_{14}N_2S_3$ requires N, 11·4; S, 39·0%). The S-*methyl* derivative was hydrolysed to 5 : 5-diethyl-2 : 4-dithiobarbituric acid by heating on the steam-bath for ½ hour with 8% hydrochloric acid, methylthiol being evolved.

4-Imino-5 : 5-diethylthiobarbituric Acid.—A solution of 5 : 5-diethyl-2 : 4-dithiobarbituric acid (2 g.) in aqueous ammonia (*d* 0·88, 20 c.c.) was warmed on the steam-bath for ½ hour; hydrogen sulphide was evolved and a yellow solid separated. After cooling, this was collected and recrystallised from methyl alcohol. It decomposed at about 220° (1·25 g.). This imino-compound was hydrolysed quantitatively to 5 : 5-diethyl-2-thiobarbituric acid (m. p. 173°) by warming for 20 minutes on the steam-bath with 4% hydrochloric acid.

Sulphurisation of Various Barbituric Acids.—A standard procedure was adopted based on that described for 5 : 5-diethylbarbituric acid. The reaction was carried out with phosphorus pentasulphide and liver of sulphur in boiling xylene, with a reaction time of 16 hours. Where mixtures of products were obtained, the separation was carried out by fractional crystallation from methyl alcohol or aqueous methyl alcohol. The results are summarised in the table. The yields recorded are only approximate, being largely dependent upon the ease of purification. In some cases, which are indicated, the higher sulphurisation products were only obtained in appreciable quantities after retreatment of the products of lower sulphur content with the sulphurising agents.

Attempts to sulphurise barbituric acids with unsaturated substituents in the 5-position were generally unsuccessful. Thus neither 5 : 5-diallylbarbituric acid nor 5-Δ³-*cyclo*hexenyl-5-ethylbarbituric acid gave identifiable products when treated in the standard way.

Barbituric acid substituents.	Thio-derivative formed.	Formula.	M. p.	Yield, %.	Analysis (%). Found. N.	Found. S.	Required. N.	Required. S.
5 : 5-Diethyl	Di	$C_8H_{12}ON_2S_2$	205—206°	20	12·9	29·7	13·0	29·6
,,	Tri	$C_8H_{12}N_2S_3$	192—193	30	12·15	40·9	12·1	41·4
5-Ethyl-5-*n*-propyl	Di	$C_9H_{14}ON_2S_2$	180	15	12·15	27·7	12·2	27·8
,,	Tri(*a*)	$C_9H_{14}N_2S_3$	177	10	11·3	38·8	11·4	39·0
5-Ethyl-5-*iso*propyl	Mono	$C_9H_{14}O_2N_2S$	189 (192)	50	13·3	15·3	13·1	15·0
,,	Di(*b*)	$C_9H_{14}ON_2S_2$	173	20	—	26·9	—	27·8
5 : 5-Di-*n*-propyl	Di	$C_{10}H_{16}ON_2S_2$	189	30	11·4	26·2	11·5	26·3
,,	Tri(*a*)	$C_{10}H_{16}N_2S_3$	205—206	20	10·7	37·2	10·75	36·9
5-Ethyl-5-*n*-butyl	Di	$C_{10}H_{16}ON_2S_2$	127	20	11·0	25·6	11·5	26·3
5-Ethyl-5-*iso*butyl	Di	$C_{10}H_{16}ON_2S_2$	190	25	11·55	25·4	11·5	26·3
,,	Tri(*a*)	$C_{10}H_{16}N_2S_3$	143	5	—	36·6	—	36·9
5-Ethyl-5-α-methylbutyl	Mono	$C_{11}H_{18}O_2N_2S$	156 (157)	30	—	13·5	—	13·8
5-Ethyl-5-β-methylbutyl	Di	$C_{11}H_{18}ON_2S_2$	158	40	10·75	24·4	10·85	24·8
5 : 5-Di-*n*-butyl	Di	$C_{12}H_{20}ON_2S_2$	125	10	10·7	22·5	10·3	23·5
,,	Tri(*a*)	$C_{12}H_{20}N_2S_3$	164	5	9·6	33·6	9·7	33·3
5-Ethyl-5-*cyclo*hexyl	Mono	$C_{12}H_{18}O_2N_2S$	203 (205)	40	12·9	10·65	12·6	11·0
5-Phenyl-5-ethyl	Di	$C_{12}H_{12}ON_2S_2$	246	10	10·8	24·8	10·6	24·3
,,	Tri	$C_{12}H_{12}N_2S_3$	162—164	20	9·9	34·3	10·0	34·3
5-Benzyl-5-ethyl	Mono	$C_{13}H_{14}O_2N_2S$	180	30	10·3	12·4	10·7	12·2
,,	Di	$C_{13}H_{14}ON_2S_2$	160	15	9·9	22·9	10·05	23·0

(*a*) Obtained by resulphurising the residues from the purification of the dithio-derivative.
(*b*) Obtained by resulphurising the residues from the purification of the monothio-derivative.

The figures in parentheses in the melting-point column are the melting points given in the literature for the monothio-compounds where these are known.

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46. 2 : 4-*Diarylpyrroles. Part IV. The Formation of Acylated 5-Amino-2 : 4-diphenylpyrroles from β-Benzoyl-α-phenylpropionitrile and Some Notes on the Leuckart Reaction.*

By W. H. Davies and Maurice A. T. Rogers.

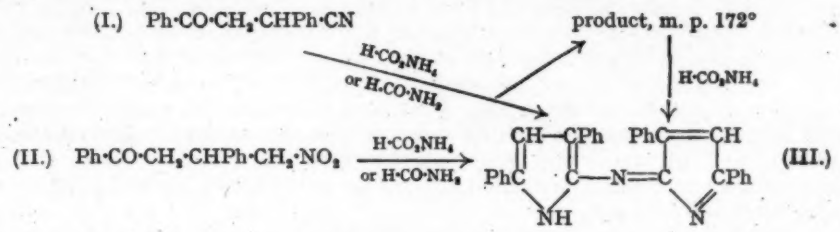
In Part I (Rogers, J., 1943, 590), the isolation of a colourless compound from the action of formamide on β-benzoyl-α-phenylpropionitrile (I) was described. This is now shown to be a formylated 5-amino-2 : 4-diphenylpyrrole. The mechanism of this reaction and of the formation of the azamethine (III) from (I) and ammonium formate or formamide are discussed and inter-related.

The mechanisms of the Leuckart reaction ($COR_2 + H{\cdot}CO_2NH_4 \longrightarrow CHR_2{\cdot}NH_2 + CHR_2{\cdot}NH{\cdot}CHO$) and of its Ott–Ingersoll modification ($COR_2 + H{\cdot}CO{\cdot}NH_2 \longrightarrow CHR_2{\cdot}NH{\cdot}CHO$) are shown to involve different intermediates which may, in the case of certain ketones, result in different products.

The *formyl* and the *acetyl* derivative of 5-amino-2 : 4-diphenylpyrrole have each been isolated in two, and the *acetyl-formyl* derivative in three, readily interconvertible isomeric forms.

In Part I (*loc. cit.*), it was shown that, when γ-nitro-β-phenylbutyrophenone (II) was heated with ammonium formate or formamide under the conditions of the Leuckart reaction, 2 : 2′ : 4 : 4′-tetraphenylazadipyrromethine (III) was formed in yields up to 33%. β-Benzoyl-α-phenylpropionitrile (I), heated with ammonium formate, also gave (III), but with formamide, only small amounts of azamethine were isolated, the main product being a colourless compound, m. p. 172°, which has now also been isolated from the action of (I) on ammonium formate. As this compound on treatment with fresh ammonium formate gave small amounts of azamethine

(III), it seemed to be a possible intermediate in the conversion of (I) into (III). It has therefore been studied in more detail in an attempt to elucidate the mechanism of these remarkable reactions.



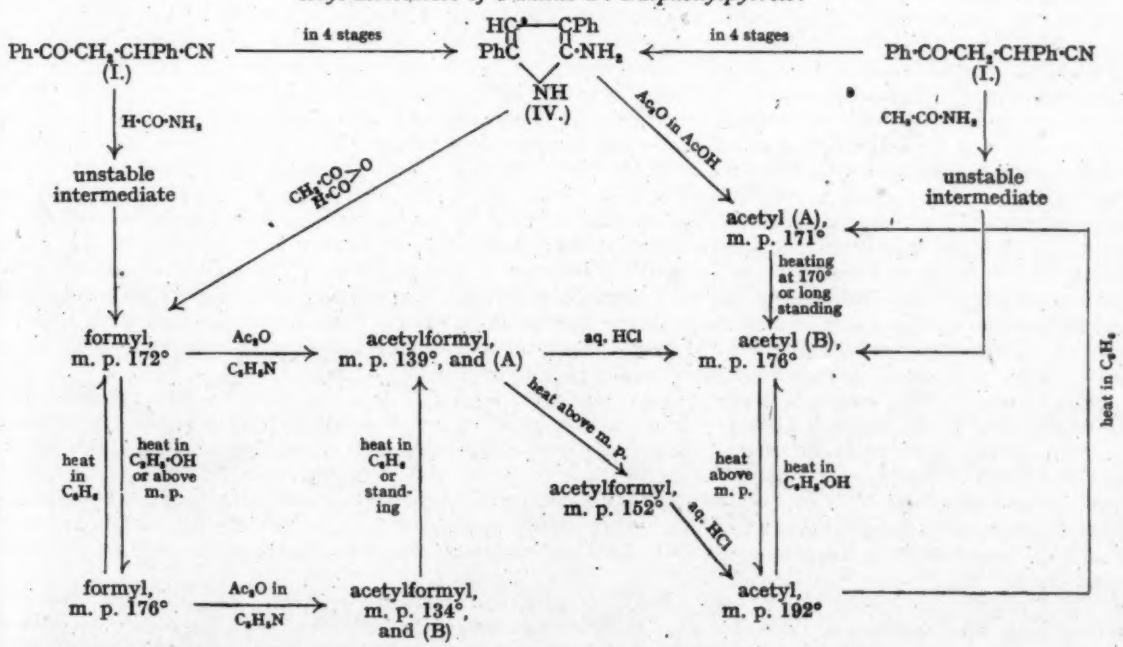
The compound, m. p. 172°, has now been identified as a *formyl* derivative of 5-amino-2 : 4-diphenylpyrrole and has been synthesised in good yield by treating 5-amino-2 : 4-diphenylpyrrole (IV) with the mixed anhydride of formic and acetic acids. A precursor of the compound, m. p. 172°, has also been isolated by working up the reaction mixture of the keto-nitrile (I) with formamide under anhydrous conditions, but owing to the ease with which this is converted into the formyl derivative, m. p. 172°, in the presence of a trace of water or even in moist air, it has not been identified with certainty.

Treatment of (I) with acetamide under anhydrous conditions similarly gave a very unstable compound which, in the presence of moisture, was rapidly converted into an acetyl derivative of 5-amino-2 : 4-diphenylpyrrole, which was also prepared by direct acetylation of the authentic amine obtained from (I) by the four-stage synthesis described in Part I (*loc. cit.*).

Hydrolysis of either of the acyl derivatives with strong mineral acid surprisingly gave β-benzoyl-α-phenylpropionic acid. This recalls the hydrolysis of 2 : 6-diaminopyridine with 70% sulphuric acid to give glutaconic acid (Titov and Levin, *J. Gen. Chem. Russ.*, 1941, **11**, 9).

The identification of the acyl derivatives of (IV) was complicated by the fact that they and the acetylformyl derivative exist in more than one form. In the case of the formyl compound, for example, crystallisation from benzene or chloroform gave fine needles, m. p. 172°, which, on heating above their m. p. or on crystallising from alcohols, gave rather stouter needles, m. p. 176°, which gave no mixed m. p. depression with the material, m. p. 172°, and were readily converted into it on heating in benzene. Two isomers of the acetyl derivative were obtained and probably a third: the acetyl-formyl derivative was also obtained in three forms. The interrelationship of these isomers is summarised in the chart.

Acyl derivatives of 5-amino-2 : 4-diphenylpyrrole.

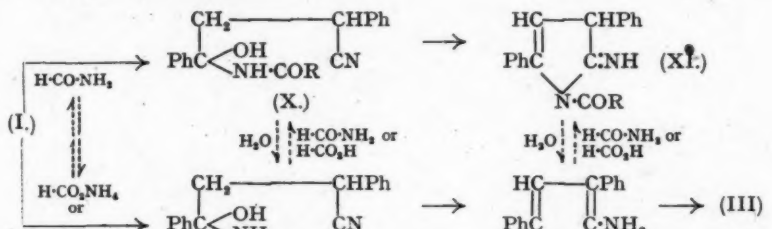


Because of the ease of isomerisation of these acyl derivatives, attempts to determine their precise structure by examining their chemical properties and ultra-violet absorption spectra were unsuccessful. (It may be mentioned that sixteen formulæ are possible for a monoacyl derivative of IV.)

We turn now to the mechanism of the formation of these acyl derivatives from the keto-nitrile (I) and amides.

Herbst and Martell (*J. Org. Chem.*, 1941, **6**, 878) showed that the action of amides, $R'\cdot CO\cdot NH_2$, on ketones, COR_2, involves direct addition to give $CR_2(OH)\cdot NH\cdot COR'$, which may then react further in various ways, according to the nature of the ketone used. In some cases, loss of water occurs; *e.g.*, in the reaction with acetamide, α-ketoglutaric acid gives an addition compound which is dehydrated to an internal lactone, whereas phenylpyruvic acid gives α-acetamidocinnamic acid as the main product (Shemin and Herbst, *J. Amer. Chem. Soc.*, 1938, **60**, 1954). Applying a similar mechanism to the present case, we consider that the first intermediate in the reaction between (I) and formamide is (X), which may indeed be the highly unstable water-sensitive product isolated by working up the reaction mixture under anhydrous conditions. By cyclising and eliminating water (cf. cyclisation of acyl derivatives of *o*-aminophenylacetonitrile to 2-aminoindoles; Pschorr and Hoppe, *Ber.*, 1910, **43**, 2543), this intermediate is converted into the acylated aminopyrrole (XI), or an isomer, which is an observed product from the reaction.

The reaction of (I) with ammonium formate, on the other hand, takes a somewhat different course. In his work on the mechanism of the Leuckart reaction, Wallach (*Annalen*, 1905, **343**, 54) showed that the reaction between ammonium formate and ketones involved dissociation of the ammonium salt, followed by formation of the ketone-ammonia $CR_2(OH)\cdot NH_2$. In the case of (I), this would lead to the formation of (XII), which, by cyclisation and dehydration, would give 5-amino-2 : 4-diphenylpyrrole (IV). It was shown, however, in Part I that this amine is readily converted into the azamethine (III) on heating in air [the yield in this conversion has now been shown to be not more than 50%; the mechanism, involving oxidation and elimination of ammonia between two moles of (IV), is still obscure]. The final product from the ammonium formate reaction is therefore not the amine (IV), but the azamethine (III).



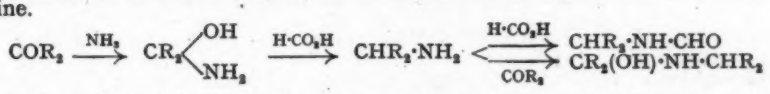
On this view, the formation of (III) in the formamide reaction is due partly to hydrolysis of (X) to (XII) and of (XI) to (IV), but mainly to the direct reaction of (I) with free ammonia formed by the thermal decomposition of formamide ($H\cdot CO\cdot NH_2 \longrightarrow CO + NH_3$). The formation of (XI) in the ammonium formate reaction is also a secondary reaction due mainly to reaction of (I) with formamide formed by dehydration of the ammonium salt on heating and to the formylating action of formamide (Hirst and Cohen, J., 1895, **67**, 829).

In agreement with this, it has been found that, from formamide and the keto-nitrile (I), the best yield of (III) is obtained by long heating at relatively low temperatures (about 120—140°). Under such conditions, formamide appears to show little tendency to react with ketones, whereas the ammonia formed by the thermal decomposition of the amide slowly gives (XII) and hence (III). At higher temperatures (above 160°), only traces of (III) can be isolated: this is because of the fairly rapid action of formamide with (I) to give (X) and hence (XI), so that the azamethine (III) is formed in such small amounts that its slow decomposition by boiling formamide (a reaction which has been observed) becomes a serious factor. The conversion of the formyl derivatives of (IV) into (III) on heating with ammonium formate is considered to be due to hydrolysis to the free amine (IV) by the water eliminated from the formate on heating. This is confirmed by the observation that the leuco-derivative of (III) is formed when the formyl compound is heated with water in a sealed tube at 180°: in the presence of air, the leuco-compound is rapidly oxidised to (III).

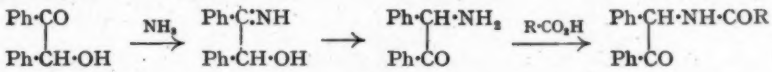
The hypothesis that ammonia is essential for converting (I) into (III) is supported by other results. When (I) is heated with salts which liberate ammonia, *e.g.*, ammonium phosphate or acetate, the azamethine is formed. Although the reaction was first discovered during dry heating with ammonium formate, it now appears that side reactions are set up, probably due to the reducing action of the free formic acid in the mixture. Better yields of the azamethine (III) are obtained by heating the reactants in alcohol, but by using the acetate in place of the formate in the dry-melt process the yields are raised to nearly 50%. A yield of 50% of (III), it should be noted, corresponds to the intermediate formation of 5-amino-2 : 4-diphenylpyrrole (IV) in theoretical yield.

These results throw light on the mechanism of the normal Leuckart reaction. Leuckart and co-workers showed that, when ketones or aldehydes were heated with ammonium formate at high temperatures, mixtures of primary, secondary and tertiary amines and their formyl derivatives were obtained (*Ber.*, 1885, **18**, 2341; 1886, **19**, 2128; 1887, **20**, 104; 1889, **22**, 1851, 2409; *J. pr. Chem.*, 1890, **41**, 330). Wallach (*loc. cit.*) found that the reaction could be carried out at much lower temperatures (100—150°) and that the addition of acid (formic or acetic) tended to give the amine formates instead of the formyl-amines. He showed that the mechanism involved formation of the ketone-ammonia, which was then reduced by the free formic acid in the

melt to give the primary amine, which might then be formylated or might react with more ketone and so give the secondary amine.



A similar mechanism was postulated by Davidson, Weiss, and Jelling (*J. Org. Chem.*, 1937, **2**, 319, 328) for the reaction between ammonium acetate or formate and benzoin or benzil in acetic acid solution, though in these cases no reduction takes place because the ketone-ammonia rearranges to desylamine, the acyl derivatives of which are amongst the observed products.



Ott (*Annalen*, 1931, **488**, 186) found that in certain cases formamide could replace ammonium formate in the reaction and gave improved yields of the formyl derivative of the primary amine: this he considered to be due to the good solvent action of the amide. Ingersoll and co-workers (*J. Amer. Chem. Soc.*, 1936, **58**, 1808) showed that this formamide modification was of general application and gave products remarkably free from secondary and tertiary amines and their derivatives. As ammonium formate is known to be dehydrated to formamide above 160° (*i.e.*, under the conditions of the normal Leuckart reaction), they postulated that formamide was the active agent in the formate reaction.

Wegler and Rüber (*Ber.*, 1935, **68**, 1053) discovered that formomethylamide also reacted with ketones and gave formyl derivatives of secondary amines. This was confirmed and extended by Novelli (*J. Amer. Chem. Soc.*, 1939, **61**, 520), who, in a later paper on the action of *N*-substituted formamides on benzoin (*Anal. Asoc. Quím. Argentina*, 1939, **27**, 151), agreed with Ingersoll's hypothesis that formamide was the active agent in the formate reaction and suggested that the mechanism for both forms of the Leuckart reaction involved addition of the amide to the ketone, to give $CR_2(OH)\cdot NH\cdot CHO$.

From the present work, it seems clear that, although formamide reacts in the way suggested by Novelli to give $CR_2(OH)\cdot NH\cdot CHO$, ammonium formate can, to some extent at least, give $CR_2(OH)\cdot NH_2$ as suggested by Wallach. It therefore follows that Ingersoll's hypothesis that formamide is the active agent in both cases is incorrect. This dual mechanism is in agreement with the fact that the formation of free amines has not been reported by the workers on the formamide reaction * (Ott, Ingersoll, Novelli, *locc. cit.*), whereas the formation of free amines in the ammonium formate reaction is well established (Leuckart, Wallach, *locc. cit.*). Further, the formamide reaction gives almost entirely the formyl derivative of the primary amine only: the frequently reported formation of secondary and tertiary amines and their derivatives in the ammonium formate reaction is undoubtedly due, as shown by Wallach, to the formation of the non-volatile amines, $CR_2(OH)\cdot NH_2$ and $CHR_2\cdot NH_2$, which compete with ammonia in the reaction with more ketone.

It should, however, be emphasised that when the Leuckart reaction is carried out above the temperature at which ammonium formate is dehydrated to formamide (*i.e.*, above about 150°), the ketone is reacting with a mixture of the amide and the ammonium salt so that both reaction mechanisms are involved, giving $CR_2(OH)\cdot NH_2$ and $CR_2(OH)\cdot NH\cdot CHO$.

From the different mechanisms involved in the Leuckart reaction and in the Ott–Ingersoll modification, it is therefore to be expected that the two methods may sometimes give rise to different products. Furthermore, "abnormal" products may be formed when the primary addition compound from either reaction is of such a type that it may be dehydrated or cyclised instead of being reduced by the free formic acid or formamide in the usual way (cf. Emerson *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 972). In cases in which the reducing action is undesirable, acetamide or ammonium acetate may show considerable advantage over the lower homologues, as has been shown in the present work with the keto-nitrile (I).

Experimental.

Melting points were taken in Pyrex tubes and are uncorrected.

The analyses are by Mr. E. S. Morton, who found that, owing to the tendency for low carbon values in this series (see Part III; Rogers, J., 1943, 598), it was advisable to mix the compounds with freshly ignited coarse copper oxide before combustion.

1. *Reactions of 5-Amino-2 : 4-diphenylpyrrole* (IV).—5-Nitroso-2 : 4-diphenylpyrrole (2 g.) in methyl alcohol (50 c.c.) was catalytically reduced to the amine (IV) as described in Part I, and the catalyst filtered off.

(a) *Formylation.* The alcoholic solution of (IV) was treated with the mixed anhydride of formic and acetic acids (5 c.c.) (cf. Béhal, G.P. 113,165, from Friedländer, vol. 6, p. 1279) and poured into water after ½ hour. The purple solid was crystallised from methyl alcohol, a small amount of azamethine (III) being removed by hot filtration. Needles of the high-melting form of formylated 5-amino-2 : 4-diphenylpyrrole separated on cooling; m. p. 173—175° (yield 1·3 g., 66%). Further crystallisation from methyl or ethyl alcohol raised the m. p. to 175—176°; crystallisation from benzene, however, gave the low-melting isomer in white felted needles, m. p. 171—172°. A mixture of the two forms had m. p. 175—176°.

(b) *Conversion into azamethine* (III). The crude amine (IV) (1·0 g.), isolated as in Part I, was heated in methyl

* An exception to this is the preparation of free amines by heating ketones with formo-β-hydroxyethylamide (Gen. Aniline, U.S.P. 2,251,245). As the amide itself is known to lose carbon monoxide readily on heating (Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079), it is probable that the intermediate $CHR_2\cdot N(C_2H_4\cdot OH)\cdot CHO$ is first formed and, under the unusually drastic reaction conditions employed in the patent example, loss of carbon monoxide follows to give the secondary amine, $CHR_2\cdot NH\cdot C_2H_4\cdot OH$.

alcohol in air for ½ hour and kept for 6 hours. The precipitated azamethine (III) was collected, washed with methyl alcohol, and dried (0·37 g., 40%). Evaporation of the red alcoholic filtrate left a resin, from which no crystalline material could be obtained.

2. *Reaction of β-Benzoyl-α-phenylpropionitrile* (I) *with Formamide.*—(a) *At various temperatures.* (I) (3 g.) (cf. Hann and Lapworth, J., 1904, **85**, 1355) and formamide (10 c.c.), heated for 17 hours, gave the following yields of azamethine (III): at 120°, 17·5%; at 140°, 18%; at 160°, 1·5%; at 180°, 0%. The yields at the higher temperatures were improved by reducing the time of heating.

(b) *At* 190°. (i) *Worked up with addition of water.* (I) (100 g.) was added to boiling formamide (100 c.c.) and heated at 185—195° (bath temperature) for 3 hours. After cooling, the paste was ground with water, collected, washed successively with very dilute hydrochloric acid, very dilute sodium hydroxide solution, and water. The purple solid was dried (107 g., m. p. 152—160°) and crystallised from benzene to give white needles (64 g.), m. p. 168—170°, identical with the *formyl* derivative of 5-amino-2 : 4-diphenylpyrrole obtained *via* the nitroso-derivative. [The benzene liquors had the purple-blue colour typical of the azamethine (III).] Further crystallisation from benzene raised the m. p. to 171—172° (Found: C, 77·45; H, 5·15; N, 10·5. $C_{17}H_{14}ON_2$ requires C, 77·85; H, 5·3; N, 10·7%).

Crystallisation of either the crude or the pure product from ethyl or methyl alcohol gave the high-melting *isomer* in coarser needles, m. p. 175—176° (Found: C, 77·45; H, 5·35; N, 10·8%).

(ii) *Worked up under anhydrous conditions.* (I) (10 g.) was added to boiling formamide (20 c.c.) and heated at 185—195° (bath temperature) for 2 hours. After cooling, the paste was collected under a current of dry nitrogen and washed with benzene (10 c.c.). The light brown solid was dissolved in hot benzene (50 c.c.), decanted from the lower layer of formamide, cleared with kieselguhr, and filtered hot. Large prisms, m. p. 145—150° (softening at 142°), separated. Two crystallisations from benzene gave white prisms, m. p. 151—154°, which after vacuum drying at 50° had m. p. 158—160° (Found: C, 73·8; H, 5·0. $C_{17}H_{14}ON_2$ requires C, 77·85; H, 5·3. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·75%).

Further crystallisation of the product gave formylated 5-amino-2 : 4-diphenylpyrrole, m. p. 171—172°, identical with previous samples (no doubt due to traces of moisture in the solvent). The crude material, m. p. 145—150°, on standing in moist air, or, more rapidly, on treatment with a trace of water, changed its crystalline form and had m. p. 167—169°; mixed m. p. with formylated 5-amino-2 : 4-diphenylpyrrole, 169—171°. No acid was liberated on treatment with water, thus indicating that the unstable intermediate is not a diformyl derivative.

(c) *In ethyl alcohol.* (I) (5·9 g.), formamide (2·5 g.), and ethyl alcohol (95 c.c.) were refluxed in a stream of air for 8 hours. The hot solution, filtered from a trace of (III), deposited (I) unchanged on cooling.

A similar experiment with (I) (3 g.) and formamide (28·7 c.c.) in alcohol (50 c.c.) gave the azamethine (III) (0·3 g., 10·7%).

3. *Reaction of β-Benzoyl-α-phenylpropionitrile* (I) *with Ammonium Formate.*—(a) *At various temperatures.* (I) (3 g.) and ammonium formate (15 g.) gave the following yields of azamethine (III) on heating in air: at 130° for ½ hour, 2·5%; at 130° for 3 hours, 24%; at 140° for 20 minutes, 7%; at 180° for 4 minutes, 5%; at 220° for 1 minute, 2·5%. In a slow stream of ammonia gas, the following yields were obtained: at 140° for 2 hours, 24%; at 160° for 20 minutes, 10·8%; at 180° for 4 minutes, 8·0%. In all cases above 160°, longer time of heating reduced the yields.

(b) *Under Leuckart conditions.* (I) (10 g.) and ammonium formate (50 g.) were heated in an open flask, allowing the water to distil off. The temperature rose to 200° in about 20 minutes. The product was worked up as in 2(b)(i), separated from the small amount of (III), and crystallised from benzene to give formylated 5-amino-2 : 4-diphenylpyrrole (2·0 g.), m. p. 171—172°.

(c) *In alcohol.* (I) (11·75 g.), ammonium formate (160 g.), and ethyl alcohol (200 c.c.) were refluxed for 20 minutes in a stream of dry air. The solution was filtered hot from the insoluble material, which was then washed twice with hot methyl alcohol to give azamethine (III) (2·36 g.). From the alcoholic filtrates, (I) was recovered (6·7 g.) (yield 21%, corresponding to a 49% conversion).

4. *Reaction of β-Benzoyl-α-phenylpropionitrile with Acetamide.*—(a) *Dry heating.* (i) *Worked up after addition of water.* (I) (10 g.) and acetamide (10 g.) were heated at 180° for 20 minutes and worked up as in 2(b) (i). Repeated crystallisation from benzene or alcohol gave fine white needles which softened at 169—170°, rehardened, and melted sharply at 192° (for details of this isomer, see Section 6b). This did not depress the m. p. of authentic acetylated 5-amino-2 : 4-diphenylpyrrole prepared *via* the nitroso-derivative (see Part I).

(ii) *Worked up under anhydrous conditions.* This was carried out as for the similar reaction with formamide [see reaction 2(b)(ii)], the crude product after purification from carbon tetrachloride having m. p. 133—139°. Repeated crystallisation slowly raised the m. p. to 171°, whereas addition of a trace of water, or standing in moist air gave a product softening at 168—170°, rehardening, and melting clear at 192°. This was identical with the product obtained in (i).

5. *Reaction of β-Benzoyl-α-phenylpropionitrile* (I) *and Ammonium Acetate.*—(a) *Dry heating.* Ammonium acetate (25 g.) and (I) (5 g.) were heated steadily in an open flask until the temperature rose to 220° (about ½ hour). The product was repeatedly extracted with hot methyl alcohol to leave the insoluble azamethine (III) (2·3 g., 48%).

(b) *In alcohol.* Ammonium acetate (7·7 g.) and (I) (4·7 g.) in alcohol (80 c.c.) were refluxed in a stream of air for 20 hours, and the azamethine isolated as in (a) (1·5 g., 38%).

6. *Action of Acetic Anhydride on the Formyl Derivatives of 5-Amino-2 : 4-diphenylpyrrole* (IV).—(a) *On formyl derivative, m. p.* 172°. The formyl derivative (crystallised from benzene) (4 g.) in pyridine (16 c.c.) was treated with acetic anhydride (8 c.c.), left overnight, and poured into water. The crude solid (4·07 g., m. p. 120—140°) crystallised from benzene in white prisms, m. p. 171—172° [mixed m. p. with the formyl derivative, 152—160°; mixed m. p. with authentic acetylated (IV) (Part I), 171—172°]. On long storage, this product no longer melted clear at 172° and slowly rehardened at this temperature to melt clear at 192—193°.

The benzene liquors from the purification of the above acetyl derivative, m. p. 172°, were treated with light petroleum (3 vols.); the precipitate crystallised from *cyclo*hexane in stout prisms of an *acetyl-formyl* derivative of (IV), m. p. 138—139° (Found: C, 74·9; H, 5·05; N, 9·1. $C_{19}H_{16}O_3N_2$ requires C, 75·0; H, 5·3; N, 9·2%). This isomer was hydrolysed with 2N-hydrochloric acid to give the acetyl derivative, m. p. 176° (see below).

After long standing in aqueous alcohol or heating with water, the acetyl-formyl compound melted at 149—151°. The same change occurred on maintaining the product at 142° ± 2° for a few minutes; the melt then solidified and remelted at 150—151°. This product was crystallised from methyl alcohol to give an *acetyl-formyl* derivative of (IV), m. p. 150—151° (alone or mixed with the isomer, m. p. 138—139°) (Found: C, 75·5; H, 5·1; N, 9·45%). On hydrolysis with 2N-hydrochloric acid, this readily gave the acetyl derivative of (IV), m. p. 192° (see below).

(b) *On formyl derivative, m. p.* 176°. The formyl derivative (crystallised from alcohol) (4 g.) was treated as in (a); the crude product (4·1 g.), m. p. 153—176°, clear at 180°, crystallised from benzene to give an *acetyl* derivative of (IV) which on slow heating showed no change before melting at 192—193°, but, when placed in a bath at 176—190°, melted clear and immediately rehardened to melt again at 191—192° (Found: C, 78·4; H, 6·0; N, 10·4. $C_{18}H_{16}ON_2$ requires C, 78·25; H, 5·8; N, 10·1%). The same m. p.'s were observed after crystallisation of the product from alcohols and the product is therefore referred to as the acetyl derivative, m. p. 176°.

This isomer was maintained at 180—185° for 3 minutes, during which time it melted and resolidified with slight

darkening to give the *acetyl* derivative of (IV), m. p. 192°. This had m. p. 189—192° and showed no signs of softening when put in a bath at 178° or 184° (Found: C, 77·9; H, 5·4; N, 10·1%).

The isomer, m. p. 192°, on heating to 200° or on crystallising from alcohol reverted to the acetyl derivative, m. p. 176°; crystallisation from benzene, however, gave the acetyl derivative, m. p. 172°. It was therefore not possible to purify this isomer further.

No mixed m. p. depressions between the isomers were obtained even when they were put in the bath at 170°.

Although it is difficult to be certain that the acetyl derivative, m. p. 172°, is not an impure form of the acetyl derivative, m. p. 176°, we believe them to be separate isomers. The chief distinction between them is the rate at which they are converted on heating into the acetyl derivative, m. p. 192°.

The benzene liquors from the purification of the acetyl derivative, m. p. 176°, were treated with light petroleum (3 vols.) to give a white solid, m. p. 134—136°, mixed m. p. with the acetyl-formyl derivative (m. p. 139°) 99—113°. On storing or on crystallising from benzene, this new acetyl-formyl derivative of (IV) was converted into the acetyl-formyl derivative, m. p. 139°. Repeated crystallisation from ligroin (b. p. 100—120°) surprisingly gave the formyl derivative, m. p. 172°, presumably by hydrolysis with a trace of moisture in the solvent. It was therefore not possible to purify this isomer for analysis.

7. *Action of Acetic Anhydride on the Acetyl Derivative of* (IV).—The acetyl compound (4·7 g.), m. p. 176°, acetic anhydride (27·5 c.c.), and sodium acetate (2·1 g.) were refluxed for 1½ hours and poured into water to give a solid (5·6 g.), m. p. 148—167°. Repeated crystallisation from alcohol or benzene gave a *diacetyl* derivative of (IV) in stout prisms, m. p. 186—188° (Found: C, 75·2; H, 5·6; N, 8·95. $C_{20}H_{18}O_5N_2$ requires C, 75·5; H, 5·7; N, 8·8%). This product shows no tendency to isomerise in different solvents or at 190°. It was not readily hydrolysed by hot 2N-hydrochloric acid.

The alcoholic liquors from the purification of the diacetyl derivative gave a second crop of crystals (0·3 g.), m. p. 106—109°. Recrystallisation from light petroleum (b. p. 40—60°) gave stout prisms of a *triacetyl* derivative of (IV), m. p. 111—112° (Found: C, 73·25; H, 5·55; N, 7·8. $C_{22}H_{20}O_6N_2$ requires C, 73·3; H, 5·55; N, 7·8%). Like the diacetyl derivative, this showed no tendency to isomerise and was resistant to acid hydrolysis.

8. *Action of Acids on the Aminopyrrole* (IV) *and its Acyl Derivatives.*—(a) *Dilute hydrochloric acid on the formyl derivative, m. p.* 172°. The formyl derivative (2·65 g.), methyl alcohol (41·2 c.c.), and 2N-hydrochloric acid (32·5 c.c.) (*i.e.*, N-hydrochloric acid in 50% methyl alcohol) were refluxed for 25 minutes. Water (100 c.c.) was added, and the clear solution treated with sodium hydrogen carbonate (5·5 g.) in water (100 c.c.). The pale yellow precipitate of the aminopyrrole (IV) was rapidly collected and washed. On exposure to air, the base became blue owing to the formation of the azamethine (III). Treatment with acetic anhydride in pyridine gave the acetyl derivative, m. p. 171°; treatment with the mixed anhydride of formic and acetic acids gave the formyl derivative, m. p. 172°, or 176° according to whether benzene or alcohol was used for purification.

(b) *Concentrated hydrochloric acid on the formyl derivative, m. p.* 172°. The formyl derivative (4·0 g.) and 36% hydrochloric acid (20 c.c.) were heated on a steam-bath for 4 hours. Water was added, and the solid collected (3·5 g., m. p. 145—146°), purified by extraction with 2N-sodium carbonate, reprecipitated, and crystallised from benzene to give β-benzoyl-α-phenylpropionic acid (2·8 g., 72%), m. p. 149—150° (decomp.) alone or mixed with authentic acid prepared by hydrolysis of (I) (Hann and Lapworth, *loc. cit.*) (Found: C, 75·45; H, 5·55. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·5%).

(c) *Concentrated hydrochloric acid on the aminopyrrole* (IV). The amine [1 g., prepared as in (a)] was treated with 36% hydrochloric acid as in (b) to give β-benzoyl-α-phenylpropionic acid (0·26 g., 24%), m. p. 150—151° (decomp.).

(d) *Concentrated hydrochloric acid on the acetyl derivative, m. p.* 171°. The acetyl compound (0·5 g.), prepared *via* the nitrosopyrrole, on similar treatment with 36% hydrochloric acid gave β-benzoyl-α-phenylpropionic acid (0·05 g., 9·3%), m. p. 149—150° (decomp.).

9. *Miscellaneous Results.*—(a) When the azamethine (III) (0·5 g.) was heated with boiling formamide (10 c.c.) for 2½ hours, the blue product was completely destroyed, giving a red solution.

(b) The formyl derivative (3 g.), m. p. 172°, was heated with water (10 c.c.) in a nitrogen-filled Carius tube at 180° for 3 hours. The product was pale blue, but, when air was passed in, rapidly became intensely blue owing to oxidation of the leuco-compound to the azamethine (III) (0·14 g., 5%). Some (1·4 g.) of the isomeric formyl derivative, m. p. 176—178°, was recovered, and amounts of formic acid (2 mols.) and ammonia (1 mol.) corresponding to the reaction $2{>}CH{\cdot}NH{\cdot}CHO \xrightarrow{2H_2O} {>}CH{\cdot}N{:}C{<} + 2H{\cdot}CO_2H + NH_3 + H_2O$ were detected in the aqueous filtrate.

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47. *Synthesis of Uronic Acids. Part II. 2 : 3 : 4-Trimethyl Derivatives of Mannuronic, Glucuronic, and Galacturonic Acids.*

By F. SMITH, M. STACEY, and P. I. WILSON.

The 2 : 3 : 4-trimethyl derivatives of mannuronic, glucuronic, and galacturonic acids have been synthesised by the oxidation of 2 : 3 : 4-trimethyl α-methylmannoside, 2 : 3 : 4-trimethyl β-methylglucoside, and 2 : 3 : 4-trimethyl α-methylgalactoside respectively with alkaline potassium permanganate.

The 2 : 3 : 4-trimethyl α-methylmannoside and the 2 : 3 : 4-trimethyl α-methylgalactoside were prepared according to the scheme: α-methylmannopyranoside (galactopyranoside) → 6-trityl α-methylmannopyranoside (galactopyranoside) → 6-*trityl* 2 : 3 : 4-*trimethyl* α-*methylmannopyranoside* (galactopyranoside) → 2 : 3 : 4-trimethyl α-methylmannopyranoside (galactopyranoside). The 2 : 3 : 4-trimethyl β-methylglucopyranoside was obtained by the methylation of 6-trityl 1 : 2 : 3 : 4-tetra-acetyl glucose, followed by the elimination of the trityl group from the 6-trityl 2 : 3 : 4-trimethyl β-methylglucopyranoside.

Each of the 2 : 3 : 4-trimethyl hexuronic acids has been identified by conversion into crystalline derivatives.

INVESTIGATIONS into polysaccharides of microbiological, plant, and animal origin have revealed the presence in these substances of uronic acids. For example, glucuronic acid is a constituent of the important pneumococcus polysaccharides (Marrack, "Chemistry of Antigens and Antibodies," 1936); it occurs in cartilage (Levene,

" Hexosamines and Mucoproteins," 1925), in gum arabic (Butler and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 1519; Weinmann, *Ber.*, 1929, **62**, 1637; Challinor, Haworth, and Hirst, J., 1931, 258; Smith, J., 1939, 1724), in mesquite gum (Anderson and Otis, *J. Amer. Chem. Soc.*, 1930, **52**, 4461; Cunneen and Smith, unpublished work), in damson gum (Hirst and Jones, J., 1938, 1174) and in cherry gum (Jones, J., 1939, 558). Galacturonic acid has been found in pectic acid (Dore, *J. Amer. Chem. Soc.*, 1926, **48**, 232; Ehrlich and Schubert, *Ber.*, 1929, **62**, 1974; Beaven and Jones, *J. Soc. Chem. Ind.*, 1939, **58**, 363; Smith, *ibid.*, p. 363; Luckett and Smith, J., 1940, 1106), in gum tragacanth (Luckett and Smith, unpublished work) and it also occurs in mucilages (Gill, Hirst, and Jones, J., 1939, 1469; Christman, Levene, and Tipson, *J. Biol. Chem.*, 1939, **128**, 609). The third uronic acid, mannuronic acid, has been identified as the main constituent of alginic acid (mannucol) (Hirst *et al.*, J., 1939, 1880). Moreover, uronic acids appear to play a predominating rôle in the determination of the specificity of polysaccharides (Goebel, *Nature*, 1939, **143**, 77). It is therefore advantageous to have methods available whereby the identity of these uronic acids can be established. One method, employed in the determination of the structure of these complex polysaccharides containing uronic acid residues, involves methylation, followed by hydrolysis. Such a procedure may lead to the formation of uronic acids in which one or more of the hydroxyl groups are substituted by methoxyl groups. In order to facilitate the identification of the three uronic acids mentioned above, we have synthesised the 2 : 3 : 4-trimethyl derivatives of *d*-glucuronic, *d*-galacturonic, and *d*-mannuronic acid.

Hexuronic acids are derived from hexoses by the oxidation of the primary alcoholic group in position 6 to a carboxyl group. Direct oxidation is not as yet practicable (Jolles, *Biochem. Z.*, 1911, **34**, 242) and poor yields of uronic acids result from the oxidation of the glycosides (Bergmann and Wolff, *Ber.*, 1923, **56**, 1060). If, however, all the hydroxyl groups in a particular hexose, with the exception of that on C_6, are suitably protected, oxidation proceeds smoothly and the corresponding uronic acid is produced. Thus the oxidation of 1 : 2 : 3 : 4-diacetone galactose with potassium permanganate in alkaline solution affords 1 : 2 : 3 : 4-diacetone galacturonic acid (Ohle and Behrend, *Ber.*, 1925, **58**, 2585). The oxidation of 1 : 2 : 3 : 4-tetra-acetyl glucose with potassium permanganate in glacial acetic acid yields 1 : 2 : 3 : 4-tetra-acetyl glucuronic acid and this in turn can be transformed into glucuronic acid (Stacey, J., 1939, 1529). Similarly oxidation of 1 : 2-monoacetone 3 : 5-benzylidene glucose with alkaline potassium permanganate gives 1 : 2-monoacetone 3 : 5-benzylidene glucuronic acid (Zervas and Sessler, *Ber.*, 1933, **66**, 1326). In view of the fact that the protecting groups in these compounds can be readily eliminated, these methods lead to the synthesis of the free uronic acids. When methylated uronic acids are required it has been found convenient to commence the synthesis with a hexose in which the hydroxyl groups, with the exception of that at C_6, are protected by methyl residues (cf. Pryde and Williams, *Biochem. J.*, 1933, **27**, 1205; Reeves, *J. Amer. Chem. Soc.*, 1940, **62**, 1616; Jones, Peat, and Owen, J., 1941, 339). In this manner 2 : 3 : 5-trimethyl galacturonic acid was prepared from 2 : 3 : 5-trimethyl methyl-galactofuranoside (Luckett and Smith, J., 1940, 1114). We have now adopted this scheme for the synthesis of the 2 : 3 : 4-trimethyl derivatives of glucuronic, mannuronic, and galacturonic acids. Oxidation of 2 : 3 : 4-trimethyl α-methylmannoside and 2 : 3 : 4-trimethyl α-methylgalactoside has yielded 2 : 3 : 4-trimethyl α-methylmannuronoside and 2 : 3 : 4-trimethyl α-methylgalacturonoside respectively, and oxidation of 2 : 3 : 4-trimethyl β-methylglucoside has given rise to the corresponding 2 : 3 : 4-trimethyl β-methylglucuronoside.

The 2 : 3 : 4-trimethyl methylhexosides required for these syntheses were obtained as follows : Treatment of α-methylmannopyranoside with trityl chloride in anhydrous pyridine gave the 6-trityl α-methylmannopyranoside and this upon methylation with methyl sulphate and sodium hydroxide afforded *6-trityl* 2 : 3 : 4-*trimethyl α-methylmannoside*. Removal of the trityl group was effected by the agency of ethereal hydrogen chloride (Smith, J., 1939, 1724), whereby there was produced the required 2 : 3 : 4-trimethyl α-methylmannopyranoside. Commencing with α-methylgalactopyranoside, the same procedure furnished 2 : 3 : 4-trimethyl α-methylgalactopyranoside. For the preparation of 2 : 3 : 4-trimethyl β-methylglucopyranoside, 6-trityl 1 : 2 : 3 : 4-tetra-acetyl glucopyranoside was subjected to direct methylation with methyl sulphate and sodium hydroxide. Detritylation of the resulting 6-trityl 2 : 3 : 4-trimethyl β-methylglucopyranoside with a solution of hydrobromic acid in glacial acetic acid (Helferich and Klein, *Annalen*, 1926, **450**, 219) gave the desired 2 : 3 : 4-trimethyl β-methylglucopyranoside.

When the 2 : 3 : 4-trimethyl α-methylmannopyranoside, the 2 : 3 : 4-trimethyl α-methylgalactopyranoside and the 2 : 3 : 4-trimethyl β-methylglucopyranoside were each treated with potassium permanganate in alkaline solution at room temperature, oxidation of the primary alcoholic group at C_6 took place and there resulted 2 : 3 : 4-trimethyl α-methylmannopyruronoside, 2 : 3 : 4-trimethyl α-methylgalactopyruronoside and 2 : 3 : 4-trimethyl β-methylglucopyruronoside respectively.

Hydrolysis of the 2 : 3 : 4-trimethyl α-methylmannuronoside with dilute hydrochloric acid yielded 2 : 3 : 4-trimethyl mannuronic acid, which upon oxidation with bromine gave 2 : 3 : 4-trimethyl mannosaccharic acid. Treatment of the latter with boiling methyl-alcoholic hydrogen chloride effected esterification and when this ester was allowed to react with methyl-alcoholic ammonia the characteristic crystalline diamide of 2 : 3 : 4-trimethyl mannosaccharic acid was produced (Haworth, Hirst, Isherwood, and Jones, J., 1939, 1878).

The 2 : 3 : 4-trimethyl derivative of glucuronic acid was identified as the crystalline 2 : 3 : 4-trimethyl β-methylglucopyruronoside (Haworth, Hirst, and Challinor, J., 1931, 258). The latter, when boiled with 3% methyl-alcoholic hydrogen chloride, was transformed into 2 : 3 : 4-trimethyl α-methylglucopyruronoside, which upon treatment with methyl-alcoholic ammonia yielded the characteristic amide of 2 : 3 : 4-trimethyl α-methylglucuronoside (Smith, *loc. cit.*).

The 2 : 3 : 4-trimethyl α-methylgalactopyruronoside was readily identified in the form of its crystalline methyl ester (Levene and Kreider, *J. Biol. Chem.*, 1937, **120**, 597; Luckett and Smith, J., 1940, 1506).

Experimental.

A. *Synthesis of* 2 : 3 : 4-*Trimethyl* α-*Methyl*-d-*mannuronoside.*

6-*Trityl* 2 : 3 : 4-*Triacetyl* α-*Methylmannoside.*—To a solution of α-methylmannopyranoside (50 g.) in dry pyridine (600 c.c.), trityl bromide (81 g.) was added and the mixture was shaken for 2 days at room temperature. Acetic anhydride (85 c.c.) was added, and the solution kept for a further 2 days at room temperature. The mixture was then poured with stirring into a large excess of cold water. The crisp yellow precipitate was collected, washed with water, and dried in the air. One crystallisation from boiling ethyl alcohol (1 l.) gave 6-trityl 2 : 3 : 4-triacetyl α-methylmannoside (94 g.). After recrystallisation from ethyl alcohol–light petroleum the compound showed m. p. 129°, $[\alpha]_D^{19°}$ + 35° in chloroform (*c*, 1·0). Treatment of this 6-trityl 2 : 3 : 4-triacetyl α-methylmannoside with hydrobromic acid in acetic acid according to the method of Helferich and Klein (*Annalen*, 1926, **450**, 219) gave 2 : 3 : 4-triacetyl α-methylmannoside, m. p. 97° (yield 80%).

6-*Trityl* 2 : 3 : 4-*Trimethyl* α-*Methylmannoside.*—6-Trityl α-methylmannoside (9·1 g.) was dissolved in acetone (60 c.c.) and methylated in the usual way with sodium hydroxide (310 c.c. of a 30% solution) and methyl sulphate (120 c.c.) at 35°. The reagents were added in tenths during 2 hours. While still being stirred, the reaction mixture was freed from acetone by heating on the water-bath. In this way the partially methylated product was obtained as a white granular mass. Two more methylations in the same way gave a white crystalline precipitate, which was collected and washed with hot water. After recrystallisation from methyl alcohol the 6-*trityl* 2 : 3 : 4-*trimethyl* α-*methylmannoside* had m. p. 149°, $[\alpha]_D^{20°}$ + 27° in chloroform (*c*, 1·05) (Found: C, 73·3; H, 7·1; OMe, 25·4. $C_{29}H_{34}O_6$ requires C, 72·9; H, 7·1; OMe, 25·9%).

2 : 3 : 4-*Trimethyl* α-*Methylmannoside.*—A solution of 6-trityl 2 : 3 : 4-trimethyl α-methylmannoside (7 g.) in ether (100 c.c.) was cooled in an ice-bath and saturated with dry hydrogen chloride. In order to remove some of the hydrogen chloride the ether was evaporated until trityl chloride began to crystallise and then the solution was extracted several times with water. The combined aqueous extracts were neutralised with lead carbonate, filtered, and evaporated under diminished pressure to dryness. Extraction of the residue with chloroform yielded 2 : 3 : 4-trimethyl α-methylmannoside as a colourless liquid (2·4 g.), b. p. (bath temp.) 130°/0·02 mm., $n_D^{24°}$ 1·4570, $[\alpha]_D^{17°}$ + 47° in water (*c*, 3·2). (Found: OMe, 50·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%) (cf. Haworth *et al.*, J., 1939, 1878).

2 : 3 : 4-*Trimethyl Mannose.*—A solution of 2 : 3 : 4-trimethyl α-methylmannoside (1 g.) in N-sulphuric acid (70 c.c.) was heated for 4 hours on the boiling water-bath. Hydrolysis had then been completed and the solution, which now showed $[\alpha]_D^{18°}$ + 10°, was neutralised with barium carbonate, filtered, and evaporated to dryness under reduced pressure. Extraction of the residue with acetone gave mainly syrupy 2 : 3 : 4-trimethyl mannose (0·88 g.), $n_D^{20°}$ 1·4780. Attempts to distil this substance in a high vacuum failed.

2 : 3 : 4-*Trimethyl* δ-*Mannonolactone.*—To a solution of 2 : 3 : 4-trimethyl mannose (0·75 g.) in water (10 c.c.), bromine (0·8 c.c.) was added. The solution was kept at room temperature for 2 days, oxidation then being complete. The solution was freed from excess of bromine by aeration, neutralised with silver oxide, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness under reduced pressure. The colourless liquid (0·71 g.) thus produced, after being heated in a high vacuum at 120°, crystallised spontaneously (cf. Haworth *et al.*, *loc. cit.*). Crystallisation of the product from acetone–light petroleum gave 2 : 3 : 4-trimethyl δ-mannonolactone as a monohydrate, m. p. 74°, $[\alpha]_D^{20°}$ + 131° (initial value in water, *c*, 1·0), changing in 170 hours to + 80°, equilibrium value (Found: C, 45·6; H, 7·8; OMe, 38·2. Calc. for $C_9H_{16}O_6,H_2O$: C, 45·4; H, 7·6; OMe, 39·1%).

2 : 3 : 4-*Trimethylmannonamide.*—The liquid 2 : 3 : 4-trimethyl δ-mannonolactone (0·15 g.) was dried by heating for 1 hour in a vacuum at 100°, and then boiled for 6 hours with 2% methyl-alcoholic hydrogen chloride. The solution was neutralised with silver carbonate, filtered, and evaporated under diminished pressure. The syrup (0·11 g.) thus obtained was dissolved in methyl alcohol, and the solution, cooled to 0°, was saturated with dry ammonia. After the solution had been kept overnight at − 5°, the excess of the solvent was removed under reduced pressure in a desiccator. Recrystallisation of the solid residue from acetone gave the amide of 2 : 3 : 4-trimethyl mannonic acid in fine needles, m. p. 142°, $[\alpha]_D^{20°}$ + 5° in water (*c*, 0·9) (Found: C, 45·4; H, 8·1; OMe, 39·9; N, 5·9. Calc. for $C_9H_{19}O_6N$: C, 45·5; H, 8·0; OMe, 39·2; N, 5·9%).

2 : 3 : 4-*Trimethylmannosaccharodiamide.*—A solution of 2 : 3 : 4-trimethyl mannose (0·32 g.) in nitric acid (9 c.c., *d* 1·42) was heated for 4 hours at 50°. The nitric acid was removed by distilling water through the solution under diminished pressure and on complete removal of the solvent a syrup (0·33 g.) was obtained which reacted strongly acid to Congo-red paper. This product was esterified by boiling it for 8 hours with 2% methyl-alcoholic hydrogen chloride (50 c.c.). Neutralisation of the mineral acid with silver carbonate, followed by removal of the solvent, gave a syrupy product, which was distilled, giving: Fraction I (0·12 g.), b. p. (bath temp.) 135°/0·03 mm., $n_D^{20°}$ 1·4560 (Found: OMe, 54·2%). Fraction II (0·12 g.), b. p. (bath temp.) 160°/0·03 mm., $n_D^{20°}$ 1·4690 (Found: OMe, 56·0. Calc. for methyl 2 : 3 : 4-trimethyl mannosaccharate: OMe, 55·4%). Treatment of fraction II with methyl-alcoholic ammonia gave the diamide of 2 : 3 : 4-trimethyl mannosaccharic acid (0·1 g.), m. p. 228°, $[\alpha]_D^{20°}$ − 16° (*c*, 0·5 in water) (after recrystallisation from ethyl alcohol–ether) (Haworth *et al.*, *loc. cit.*, record m. p. 228°, $[\alpha]_D^{20°}$ − 17° in water, for this compound).

2 : 3 : 4-*Trimethyl* α-*Methylmannuronoside.*—2 : 3 : 4-Trimethyl α-methylmannoside (2·35 g.) was dissolved in water (100 c.c.) containing potassium hydroxide (1·18 g.). To this solution a solution of potassium permanganate (3·25 g.) in water (200 c.c.) was cautiously added. The volume was adjusted to 450 c.c., and the oxidation allowed to proceed at room temperature for 3 days. The mixture was then treated with charcoal, warmed to 50°, filtered, and neutralised with carbon dioxide. The filtrate was evaporated to dryness under diminished pressure. Extraction of the residue five times with boiling methyl alcohol gave a colourless glassy solid (3·05 g.) consisting mainly of the potassium salt of 2 : 3 : 4-trimethyl methylmannuronoside. This potassium salt was converted into the corresponding methyl ester by boiling it for 10 hours with 2% methyl-alcoholic hydrogen chloride (100 c.c.). The solution was filtered to remove potassium chloride, neutralised with silver carbonate, filtered again, and evaporated to dryness under diminished pressure. Extraction of the dry residue with boiling ether gave the methyl ester of 2 : 3 : 4-trimethyl methylmannuronoside (2 g.) as a colourless liquid, b. p. (bath temp.) 118°/0·02 mm., $n_D^{18°}$ 1·4515, $[\alpha]_D^{18°}$ + 45° in chloroform (*c*, 1·0) (Found: OMe, 57·1%) (cf. Haworth, Hirst, and Ault, J., 1935, 517).

2 : 3 : 4-*Trimethylmannuronic Acid.*—A solution of the methyl ester of 2 : 3 : 4-trimethyl methylmannuronoside (0·49 g.) in N-hydrochloric acid (10 c.c.) was heated on the boiling water-bath for 7 hours. The solution, which had $[\alpha]_D^{18°}$ + 50° initially, now showed $[\alpha]_D^{18°}$ + 32° (constant value). The solution was neutralised with silver carbonate, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness under reduced pressure. The colourless viscid syrup (0·41 g.) thus produced was strongly reducing to Fehling's solution and reacted acid to Congo-red paper.

Oxidation of 2 : 3 : 4-*Trimethylmannuronic Acid by Bromine.*—To a solution of the syrupy 2 : 3 : 4-trimethylmannuronic acid (0·41 g.) in water (30 c.c.) bromine (0·7 c.c.) was added, and the mixture kept at room temperature until a test portion, when freed from bromine, no longer reduced Fehling's solution. The excess of bromine was then removed from the main bulk of the solution by aeration, and the solution neutralised with lead carbonate and filtered. Lead was removed as sulphide, and the filtrate freed from hydrogen sulphide by evaporation of some of the liquid under reduced pressure. The solution, which contained some hydrobromic acid, was neutralised with silver carbonate, filtered before and after treatment with hydrogen sulphide, and evaporated to dryness under reduced pressure. The syrup produced reacted acid to Congo-red paper, and was non-reducing to Fehling's solution (Found : equiv., 120. Calc. for 2 : 3 : 4-trimethyl mannosaccharic acid : equiv., 126). The acid was esterified by boiling with 2% methyl-alcoholic hydrogen chloride (50 c.c.) as described above. Distillation of the product gave : Fraction A (0·16 g.), b. p. (bath temp.) 135°/0·03 mm., $n_D^{20°}$ 1·4477. Fraction B (0·08 g.), b. p. (bath temp.) 150—160°/0·03 mm., $n_D^{20°}$ 1·4539. Treatment of fraction B with methyl-alcoholic ammonia in the manner previously described afforded the diamide of 2 : 3 : 4-trimethyl *d*-mannosaccharic acid, m. p. 228° (after recrystallisation from ethyl alcohol–light petroleum). This was identical with the diamide prepared directly from 2 : 3 : 4-trimethyl mannose.

B. *Synthesis of* 2 : 3 : 4-*Trimethyl β-Methyl-α-glucuronoside.*

6-*Trityl* 2 : 3 : 4-*Trimethyl β-Methylglucoside.*—6-Trityl 1 : 2 : 3 : 4-tetra-acetyl glucose (5·09 g.), prepared according to the directions given by Stacey (J., 1939, 1529), was dissolved in acetone and methylated with methyl sulphate and sodium hydroxide in the manner described previously for the methylation of 6-trityl 2 : 3 : 4-triacetyl α-methylmannoside. Five methylations gave 6-trityl 2 : 3 : 4-trimethyl β-methylglucoside as an amorphous, pale yellow powder. This was collected, washed with boiling water, and dried in a vacuum over phosphoric oxide. On removal of the trityl residue with a solution of hydrogen bromide in glacial acetic acid (Helferich and Klein, *loc. cit.*) there was obtained a syrup (1·9 g.). Purification by distillation gave a colourless liquid (1·65 g.), b. p. (bath temp.) 125—130°/0·04 mm., which underwent partial crystallisation when nucleated with 2 : 3 : 4-trimethyl β-methylglucoside. After draining on a porous tile, followed by recrystallisation from ether–light petroleum, the 2 : 3 : 4-trimethyl β-methylglucoside (0·82 g.) had m. p. and mixed m. p. 87°.

2 : 3 : 4-*Trimethyl β-Methylglucuronoside.*—To a solution of 2 : 3 : 4-trimethyl β-methylglucoside (1·0 g.) in water (50 c.c.) containing 0·1N-sodium hydroxide (10 c.c.) was added a solution of potassium permanganate (1 g.) in water (50 c.c.) during 7 hours at room temperature. After 30 hours the solution was treated with a little charcoal, filtered, neutralised with carbon dioxide, and evaporated to dryness under reduced pressure. A small amount of unchanged 2 : 3 : 4-trimethyl β-methylglucoside (*ca.* 50 mg.) was removed by extraction of the dry residue with chloroform. The residue was analysed for potassium and the exact amount of 0·1N-sulphuric acid required to convert the potassium into potassium sulphate was added. The solution was extracted several times with chloroform, and the combined extracts dried over anhydrous magnesium sulphate. Removal of the solvent gave crystalline 2 : 3 : 4-trimethyl β-methylglucuronoside (0·6 g.), m. p. and mixed m. p. 137° after recrystallisation from ether–light petroleum (Found : C, 47·8; H, 7·5; OMe, 48·8. Calc. for $C_{10}H_{18}O_7$: C, 47·8; H, 7·2; OMe, 49·4%). Esterification of this uronic acid by boiling with 2% methyl-alcoholic hydrogen chloride gave the methyl ester of 2 : 3 : 4-trimethyl methylglucuronoside as a liquid, from which the crystalline amide of 2 : 3 : 4-trimethyl α-methylglucuronoside was prepared by the action of methyl-alcoholic ammonia. This amide had m. p. and mixed m. p. 181° (after crystallisation from ethyl alcohol–ether).

C. *Synthesis of* 2 : 3 : 4-*Trimethyl α-Methyl-α-galacturonoside.*

To an ice-cold solution of potassium permanganate (3·0 g.) and potassium hydroxide (1·0 g.) in water (200 c.c.) there was slowly added during 1 hour a solution of 2 : 3 : 4-trimethyl α-methylgalactoside (2 g.) (prepared by the method of Smith, J., 1939, 1736) in water (30 c.c.). The ice-bath was removed, and the reaction mixture kept at room temperature for 3 days; all the permanganate had then been used up. The mixture was treated with a little charcoal, warmed to 50°, and filtered. The filtrate was neutralised with carbon dioxide, concentrated in a vacuum to half volume, and neutralised with dilute sulphuric acid, with methyl-orange as indicator. To this neutral solution N-sulphuric acid (8·0 c.c.) was added to liberate the organic acid and the solution was evaporated to dryness under diminished pressure. Extraction of the residue with chloroform, followed by removal of the solvent, gave an acidic syrup, which was esterified by boiling for 8 hours with 1% methyl-alcoholic hydrogen chloride (50 c.c.). Neutralisation of the mineral acid with silver carbonate, followed by removal of the excess of the solvent under diminished pressure, gave a colourless liquid which crystallised immediately upon nucleation with a specimen of the methyl ester of 2 : 3 : 4-trimethyl α-methylgalacturonoside prepared from galacturonic acid. The product was purified by distillation, b. p. 130°/0·03 mm. (yield, 1·5 g.). The distillate crystallised spontaneously and after recrystallisation from ether the methyl ester of 2 : 3 : 4-trimethyl α-methylgalacturonoside had m. p. and mixed m. p. 73°, $[\alpha]_D^{21°}$ + 169° in water (*c*, 0·65) (Found : C, 50·15; H, 7·7; OMe, 58·0. Calc. for $C_{11}H_{20}O_7$: C, 50·0; H, 7·65; OMe, 58·7%).

Treatment of the ester with methyl-alcoholic ammonia in the usual manner gave the amide of 2 : 3 : 4-trimethyl α-methylgalacturonoside, which was recrystallised from acetone–ether; m. p. and mixed m. p. with an authentic specimen 152°, $[\alpha]_D^{20°}$ + 120° (chloroform, *c*, 1·0) (cf. Levene and Kreider, *J. Biol. Chem.*, 1937, **121**, 158).

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48. *Studies in the Polyene Series. Part XII. Ethynylcarbinols from Sorbaldehyde and Octatrienal. Poly-carbon Anionotropic Rearrangements.*

By I. M. HEILBRON, E. R. H. JONES, and J. T. MCCOMBIE.

Ethynylcarbinols (I and II) are prepared from sorbaldehyde and octatrienal by reaction with sodium acetylide in liquid ammonia. On treatment with dilute sulphuric acid five- and seven-carbon anionotropic rearrangements yield conjugated *dienyne-* (IV) and *trienyne-carbinols* (V) which after complete hydrogenation, and oxidation of the saturated carbinols, give methyl hexyl and methyl octyl ketones respectively. Insofar as the location of the absorption maximum is concerned, replacement of an ethenoid linkage in a conjugated polyene by an acetylenic bond has a negligible effect.

IT has already been demonstrated (Jones and McCombie, J., 1942, 733) that ethynylcarbinols can be prepared from αβ-unsaturated aldehydes by condensation with sodium acetylide in liquid ammonia solution, and this

method has now been extended to condensations with polyene aldehydes. From sorbaldehyde there is obtained a 50% yield of *octa*-4 : 6-*dien*-1-*yn*-3-*ol* (I), the light absorption of which (Fig. 1 and table) is typical, both in location and intensity of the maximum, of the conjugated diene system. Similarly, octatrienal gives the crystalline *deca*-4 : 6 : 8-*trien*-1-*yn*-3-*ol* (II) (m. p. 73·5—74·5°) in 30% yield, the carbinol exhibiting an absorption spectrum (Fig. 2 and table) practically identical with that of octatrienol (III).

$CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}C{\vdots}CH$ (I.)
$CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}C{\vdots}CH$ (II.)
$CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OH$ (III.)

In the presence of acids both (I) and (II) undergo facile anionotropic rearrangements analogous to those already described (Jones and McCombie, J., 1943, 261) with propenylethynyl and similar carbinols from αβ-unsaturated aldehydes. Thus, *octa*-3 : 5-*dien*-1-*yn*-7-*ol* (IV) is produced in good yield when the ethynylcarbinol (I) from sorbaldehyde is shaken with 5% sulphuric acid, its constitution being readily established by complete

FIG. 1.

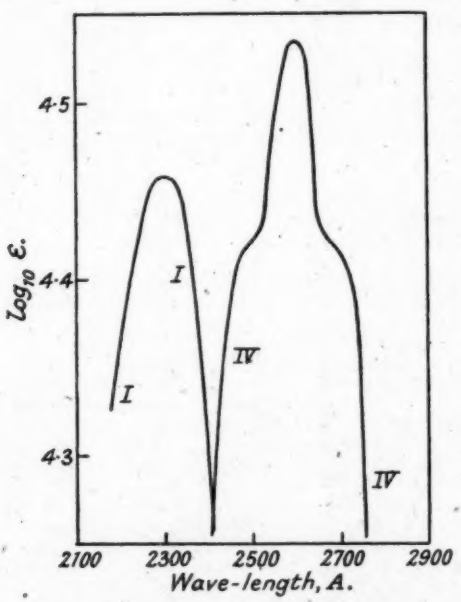
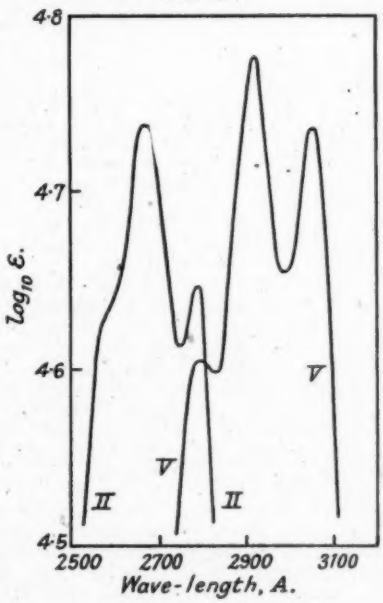


FIG. 2.



hydrogenation and oxidation of the saturated carbinol to methyl hexyl ketone. The ethynylcarbinol (II) is converted on shaking in ethereal solution with 2·5% sulphuric acid into *deca*-3 : 5 : 7-*trien*-1-*yn*-9-*ol* (V) (m. p. 82—83°), which on hydrogenation and subsequent oxidation yields methyl octyl ketone.

$CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}C{\vdots}CH$ (IV.)
$CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}C{\vdots}CH$ (V.)
$CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OH$ (VI.)

The absorption spectra of the two isomerised carbinols (IV) and (V) (Figs. 1 and 2 and table), are in accord with previous observations on conjugated polyenyne systems (Parts VIII—XI, J., 1943, 261—270). The unsymmetrical dienyne system present in the carbinol (IV), the symmetrical dienyne systems of 7-methylnona-3 : 7-dien-5-yn-2-ol (VII) and deca-3 : 7-dien-5-yn-2 : 9-diol (VIII) and

$CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}C{\vdots}C{\cdot}CMe{:}CH{\cdot}CH_3$ (VII.)
$CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}C{\vdots}C{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_3$ (VIII.)

the triene system of octatrienol all exhibit maximal intensities in the region 2600—2675 A. Again, the carbinol (V), containing the conjugated trienyne system, and decatetraenol (VI) both absorb most strongly at about 2950 A. From the evidence now available it is possible to make the generalisation that, insofar as the location of the absorption maximum is concerned, the replacement of an ethenoid linkage of a conjugated polyene system by an acetylenic bond has a negligible effect. As has previously been pointed out, however, and as is further illustrated in the examples given in the table, marked effects on the intensity of absorption are observed although these become less obvious as the size of the polyene system increases.

The literature furnishes but little information concerning anionotropic rearrangements other than those involving the familiar three-carbon system and there are no instances recorded of five- and seven-carbon migrations of hydroxyl groups. The closest approach to analogy with the isomerisations now described is the rearrangement of 1 : 2-dibromohexa-3 : 5-diene to the 1 : 6-isomer in the presence of hydrogen bromide or merely on heating (Farmer, Laroia, Switz, and Thorpe, J., 1927, 2937). It is somewhat surprising that, in spite of the known lability of compounds such as phenylpropenylcarbinol, no attempts have been made to

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Octa-4 : 6-dien-1-yn-3-ol (I) (Fig. 1)	2300	28,500
Octa-3 : 5-dien-1-yn-7-ol (IV) (Fig. 1)	2600	34,000
	2470 *	24,500
	2730 *	24,500
7-Methylnona-3 : 7-dien-5-yn-2-ol [1] (VII)	2640	16,500
Deca-3 : 7-dien-5-yn-2 : 9-diol [2] (VIII)	2650	21,500
	2800	19,000
Deca-4 : 6 : 8-trien-1-yn-3-ol (II) (Fig. 2)	2675	55,000
	2780	44,500
	2580 *	43,000
Octatrienol [1] (III)	2645	53,000
	2760	46,500
	2560	42,500
Deca-3 : 5 : 7-trien-1-yn-9-ol (V) (Fig. 2)	2920	60,000
	3050	54,000
	2790	40,000
Decatetraenol [3] (VI)	2985	64,000
	3110	64,000

* Inflexion.

[1] Heilbron, Johnson, Jones, and Raphael, J., 1943, 265.
[2] Heilbron, Jones, and Raphael, J., 1943, 268.
[3] Reichstein and Trivelli, *Helv. Chim. Acta*, 1932, **15**, 1074.

examine the possible extension of anionotropic systems of this type to include the condensation products of sorbaldehyde and octatrienal with phenylmagnesium bromide.

Experimental.

(Absorption spectra were determined in alcoholic solutions.)

Octa-4 : 6-dien-1-yn-3-ol (I).—Sodium (8·4 g.) was gradually added with stirring to liquid ammonia (500 c.c.) through which a rapid stream of acetylene was passing, and when addition was complete a solution of sorbaldehyde (35 g.) in ether (125 c.c.) was dropped in during an hour. Stirring was continued for a further 4 hours, the acetylene replaced by nitrogen, the mixture treated with ammonium chloride (19·5 g.), and the ammonia allowed to evaporate off overnight. The product was isolated by means of ether and two distillations gave *octa-4 : 6-dien-1-yn-3-ol* (24 g.), as a colourless oil which rapidly darkens on standing; b. p. 71—74°/0·5 mm., $n_D^{20°}$ 1·5126 (Found: C, 78·5; H, 8·1. $C_8H_{10}O$ requires C, 78·7; H, 8·2%). A naphthylurethane or other derivative could not be prepared, probably owing to the instability of the carbinol.

Octa-3 : 5-dien-1-yn-7-ol (IV).—A mixture of the above carbinol (10 g.) and sulphuric acid (50 c.c., 5% w/v), together with a trace of quinol, was shaken under nitrogen for 12 hours at 20°. Isolation by means of ether gave *octa-3 : 5-dien-1-yn-7-ol* (6 g.) as a colourless oil which darkens rapidly on standing; b. p. 62—65°/0·5 mm., $n_D^{16°}$ 1·5468. With a solution of antimony trichloride in chloroform, both this carbinol and its isomeride give transient blue colorations which quickly change to black (Found: C, 78·8; H, 8·0. $C_8H_{10}O$ requires C, 78·7; H, 8·2%).

Methyl Hexyl Ketone.—A solution of (IV) (1·4 g.) in ethyl acetate (30 c.c.) was shaken with hydrogen in the presence of platinic oxide (100 mg.) until absorption was complete. The catalyst and solvent were removed, the latter through a column, and the residual carbinol was oxidised with chromic acid to methyl hexyl ketone; semicarbazone, m. p. 121—122° (Bouveault and Locquin, *Bull Soc. chim.*, 1904, **31**, 1157, give m. p. 122°); 2 : 4-dinitrophenylhydrazone, m. p. 58—59° (Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2957, gives m. p. 58°). Neither of these derivatives depressed the m. p. of an authentic specimen.

Deca-4 : 6 : 8-trien-1-yn-3-ol (II).—This was prepared by the method described above [sodium (2·7 g.) and octatrienal (14 g.)] with the difference that, after the addition of ammonium chloride, the ammonia was evaporated off during 2 hours. Distillation of the product isolated by means of ether gave a pale yellow oil, b. p. 94—96°/1 mm., which readily solidified, and on crystallisation from light petroleum (b. p. 60—80°), *deca-4 : 6 : 8-trien-1-yn-3-ol* (5 g.) was obtained as long colourless needles, m. p. 73·5—74·5° (Found: C, 81·0; H, 8·35. $C_{10}H_{12}O$ requires C, 81·1; H, 8·1%). *Active hydrogen* (Zerewitinoff): the carbinol (101 mg.) evolved 33·1 c.c. of methane at 23°/754 mm., equivalent to 2·0 active hydrogen atoms per mol. The carbinol is very sensitive to atmospheric oxidation, a brown resin being formed. With a solution of antimony trichloride in chloroform it gives a transient purple coloration rapidly changing to green.

Deca-3 : 5 : 7-trien-1-yn-9-ol (V).—A solution of (II) (1 g.) in ether (10 c.c.) containing a trace of quinol was shaken with sulphuric acid (20 c.c.; 2·5% w/v) in the dark in an atmosphere of nitrogen at 20° for 22 hours. Isolation in the usual manner gave a crystalline product from which *deca-3 : 5 : 7-trien-1-yn-9-ol* (0·5 g.) was obtained from light petroleum (b. p. 60—80°) as colourless needles, m. p. 82—83° (Found: C, 81·15; H, 8·2. $C_{10}H_{12}O$ requires C, 81·1; H, 8·1%). The carbinol is unstable in air. With a solution of antimony trichloride in chloroform it gives a transient purple coloration rapidly becoming green.

Methyl Octyl Ketone.—A solution of (V) (0·4 g.) in ethyl acetate (35 c.c.) was shaken with hydrogen in the presence of platinic oxide (100 mg.) until absorption was complete. Oxidation of the resulting saturated carbinol with chromic acid yielded methyl octyl ketone, which gave a semicarbazone, m. p. 121—122° (Pickard and Kenyon, J., 1911, **99**, 57, give m. p. 121°), undepressed on admixture with an authentic specimen.

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Imperial College of Science and Technology, London, S.W.7. [*Received, November 3rd*, 1943.]

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49. *Studies in the Polyene Series. Part XIII. Acetylenyl Glycols from Polyene Aldehydes and their Rearrangement with Acids.*

By I. M. Heilbron, E. R. H. Jones, and R. A. Raphael.

Acetylenyl glycols (II; $n = 2$ and 3) are prepared from sorbaldehyde (I; $n = 2$) and octatrienal (I; $n = 3$) in 42 and 20% yields respectively. On treatment with acids these glycols undergo dual anionotropic rearrangements giving conjugated polyenyne glycols (III; $n = 2$ and 3), the constitutions of which are proved by complete hydrogenation, followed by hypobromite oxidation of the saturated glycols to known C_{12} and C_{16} dicarboxylic acids. The rearranged glycols, which are both yellow, closely resemble corresponding members of the polyene series in their light-absorption properties.

We have already described the preparation of the acetylenyl glycol from crotonaldehyde and certain of its properties (J., 1943, 268). The Grignard method has now been found to be applicable to the synthesis of acetylenyl glycols from the polyene aldehydes, sorbaldehyde (I; $n = 2$) and octatrienal (I; $n = 3$). Condensation of the former with acetylenyldimagnesium bromide gave the acetylenyl glycol, *tetradeca*-2 : 4 : 10 : 12-*tetraen*-7-*yn*-6 : 9-*diol* (II; $n = 2$) in 42% yield as a colourless crystalline solid, m. p. 95—102°. The wide melting-point range probably indicates that the product is a mixture of isomers, a number of which (stereo and geometrical) are obviously possible. Its light absorption (Fig. 1 and Table I) may be compared with that of a

Fig. 1.

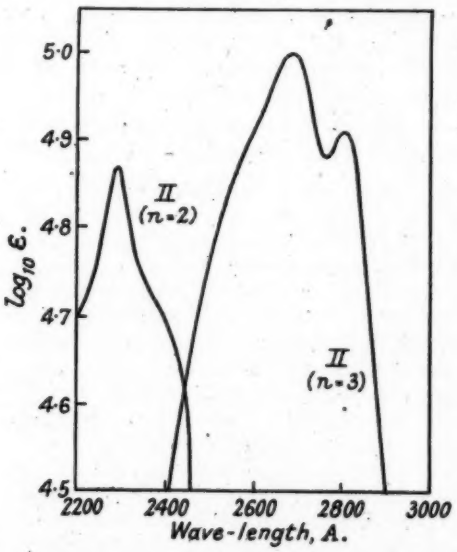
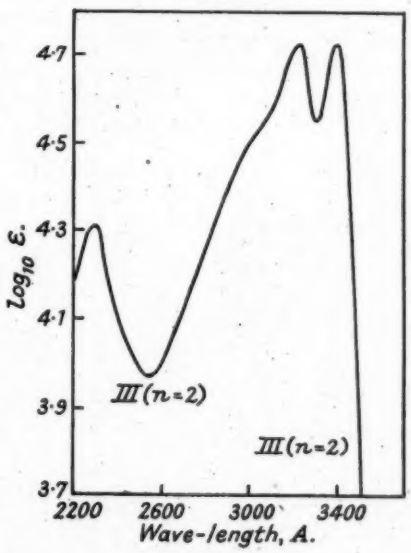


Fig. 2.



simple diene system, the intensity being considerably accentuated by the presence of two such systems in one and the same molecule. With maleic anhydride it readily formed a solid adduct which, however, was too

$$CH_3\cdot[CH{:}CH]_n\cdot CHO \quad (I.)$$

$$CH_3\cdot[CH{:}CH]_n\cdot CH(OH)\cdot C{\equiv}C\cdot CH(OH)\cdot[CH{:}CH]_n\cdot CH_3 \quad (II.)$$

$$\downarrow \text{acids}$$

$$CH_3\cdot CH(OH)\cdot[CH{:}CH]_n\cdot C{\equiv}C\cdot[CH{:}CH]_n\cdot CH(OH)\cdot CH_3 \quad (III.)$$

sparingly soluble to be purified. Zerewitinoff determinations on this and all other glycols described in this paper gave the expected values of two active hydrogen atoms.

In the same manner octatrienal (I; $n = 3$) gave *octadeca*-2 : 4 : 6 : 12 : 14 : 16-*hexaen*-9-*yn*-8 : 11-*diol* (II; $n = 3$), m. p. 154°, in 20% yield, accompanied by a considerable quantity of tarry material, presumably containing some stereoisomers. The locations of the absorption maxima (Fig. 1 and Table I) are similar to

Table I.

(Solutions in alcohol.)

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Tetradeca-2 : 4 : 10 : 12-tetraen-7-yn-6 : 9-diol (II; $n = 2$) (Fig. 1)	2290	74,000		2580 *	43,000
	2370 *	54,000	Deca-4 : 6 : 8-trien-1-yn-3-ol [1]	2675	55,000
Octa-4 : 6-dien-1-yn-3-ol [1]	2300	28,500		2780	44,500
1 : 6-Diacetoxyhexa-2 : 4-diene [2]	2280	27,500		2560	42,500
Octadeca-2 : 4 : 6 : 12 : 14 : 16-hexaen-9-yn-8 : 11-diol (II; $n = 3$) (Fig. 1)	2690	100,000	Octatrienol [3]	2645	53,000
	2810	81,000		2780	46,500

* Inflexions.

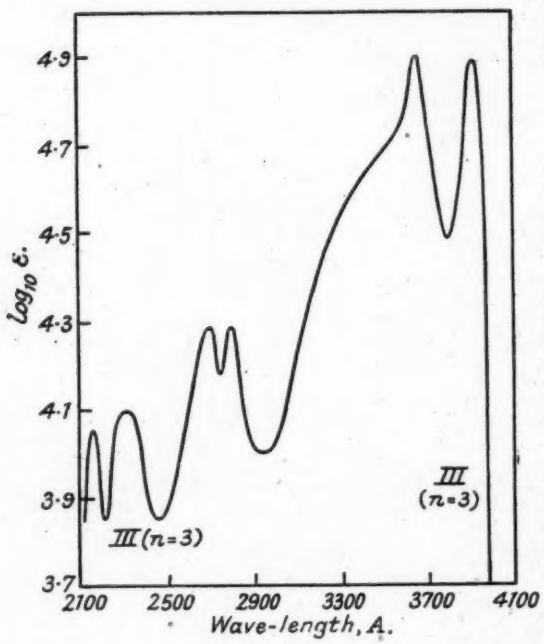
[1] Heilbron, Jones, and McCombie, preceding paper.
[2] Booker, Evans, and Gillam, J., 1940, 1453.
[3] Heilbron, Johnson, Jones, and Raphael, J., 1943, 265.

those of carbinols containing the conjugated triene chromophore but their intensities are, of course, considerably higher.

The rearrangements of the ethynylcarbinols from sorbaldehyde and octatrienal, yielding conjugated polyenyne carbinols have already been reported (previous paper); by similar but dual anionotropic rearrangements of the above glycols (II; $n = 2$ and 3) in the presence of acids, symmetrical conjugated polyenyne glycols (III; $n = 2$ and 3) should be produced, substances of considerable interest because of their approach to caro-

tenoid structures. When an ethereal solution of the glycol (II; $n = 2$) from sorbaldehyde was shaken with 5% sulphuric acid, the isomeric glycol, *tetradeca*-3 : 5 : 9 : 11-*tetraen*-7-*yn*-2 : 13-*diol* (III; $n = 2$), containing the symmetrical conjugated tetraenyne system, was isolated in 25% yield. The comparatively low yield is probably due to the fact that the product appears to be a single stereoisomer. It was obtained as crystals, m. p. 115—116°, which were colourless when viewed by transmitted light, but pale yellow in reflected light. Previous work in this field (preceding paper) indicates that the polyene and polyenyne series are closely allied as far as light-absorption properties are concerned. Consequently, the appearance of colour in the glycol (III; $n = 2$) is to be expected, since the closely related tetradecapentaenol (IV) is described by Kuhn and Grundmann (*Ber.*, **1938**, **71**, 442) as crystallising in straw-yellow leaflets, and pure crystalline vitamin A (Baxter and Robeson, *J. Amer. Chem. Soc.*, **1942**, **64**, 2411) and the crystalline farnesinol (V) (Fischer and Hultzsch, *Ber.*, **1935**, **68**, **1733**), all containing the conjugated pentadienol system, are pale yellow.

FIG. 3.



$CH_3 \cdot [CH{:}CH]_5 \cdot CH(OH) \cdot CH_2 \cdot CH_3$ (IV.)
$CMe_2{:}CH \cdot CH{:}CH \cdot CMe{:}CH \cdot CH{:}CH \cdot CMe{:}CH \cdot CH_2 \cdot OH$ (V.)

Also, Kuhn and Grundmann (*loc. cit.*) observed that in the series of dimethylpolyenes, $CH_3 \cdot [CH{:}CH]_n \cdot CH_3$, whereas 1 : 8-dimethyloctatetraene ($n = 4$) is colourless, 1 : 12-dimethyldodecahexaene ($n = 6$) is yellow.

The glycol (II; $n = 3$) from octatrienal could not be isomerised completely in a heterogeneous medium, but a solution in alcohol or acetone containing some 10% sulphuric acid gradually became yellow, and after 24 hours the rearranged glycol, *octadeca*-3 : 5 : 7 : 11 : 13 : 15-*hexaen*-9-*yn*-2 : 17-*diol* (III; $n = 3$) was isolated in 80% yield as lemon-yellow needles, m. p. 149°.

The structures of both glycols (III; $n = 2$ and 3) were proved by complete hydrogenation by means of Adams's catalyst, followed by oxidation of the saturated 2 : 13- and 2 : 17-glycols with hypobromite to decane-1 : 10-dicarboxylic and tetradecane-1 : 14-dicarboxylic (thapsic) acids, respectively.

The similarity in colour between the isomerised glycols and corresponding polyenes has already been discussed and, as would be expected, the complete absorption spectra are closely analogous (Figs. 2 and 3; Table II).

TABLE II.

(Solutions in alcohol.)

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Tetradeca-3 : 5 : 9 : 11-tetraen-7-yn-2 : 13-diol (III; $n = 2$) (Fig. 2)	2280	20,000	1 : 12-Dimethyldodecahexaene [5] (in $CHCl_3$ *)	3280	25,000
	3230	54,000		3400	46,000
	3410	54,000		3600	69,500
Vitamin A [4]	3280	51,000		3750	49,500
Octadeca-3 : 5 : 7 : 11 : 13 : 15-hexaen-9-yn-2 : 17-diol (III; $n = 3$) (Fig. 3)	2150	11,000	Dihydro-α-crocetin [6] (VI)	3470	59,000
	2310	13,000		3650	74,000
	2700	19,500		3860	64,500
	2800	19,500	Dihydrobixin methyl ester [6] (VII)	3870	56,000
	3650	79,500		4070	79,000
	3920	78,500		4310	67,500

* Main max. probably at about 3550 A. in alcohol.

[4] Baxter and Robeson, *J. Amer. Chem. Soc.*, 1942, **64**, 2411.
[5] Kuhn, *Angew. Chem.*, 1937, **50**, 703.
[6] Euler, Karrer, Klussman, and Morf, *Helv. Chim. Acta*, 1932, **15**, 504.

No absorption data for a conjugated heptaene system are available, and consequently the spectrum (Fig. 3) of the rearranged glycol (III; $n = 3$) from octatrienal has to be compared with those of dihydro-α-crocetin (VI) and the methyl ester of dihydrobixin (VII), containing six and eight conjugations, respectively. Such a comparison is not strictly justified, for Kuhn and Grundmann (*Ber.*, **1937**, **70**, **1318**) have observed that in the case of carotenoid polyenes the presence of a substituent methyl group on the polyene chain causes displacement

$CO_2H \cdot CHMe \cdot CH{:}CH \cdot CH{:}CMe \cdot CH{:}CH \cdot CH{:}CH \cdot CMe{:}CH \cdot CH{:}CH \cdot CHMe \cdot CO_2H$ (VI.)
$CO_2Me \cdot CH_2 \cdot [CH{:}CMe \cdot CH{:}CH]_2 \cdot [CH{:}CH \cdot CMe{:}CH]_2 \cdot CH_2 \cdot CO_2Me$ (VII.)

of the absorption maxima to longer wave-lengths, the increase being of the order of 50 A. for each such group. If this " correction " be applied to the main absorption maxima of (VI) and (VII) (containing two and four

side-chain methyl groups respectively), the values 3550 A. and 3870 A. respectively are obtained. In the preceding paper it was observed that, as far as the locations of the maxima are concerned, the absorption spectra of polyenes are but little affected by replacing one of the ethylenic linkages by an acetylenic linkage and it is again apparent that the intensity differences, so marked in the simple conjugated vinyl- and divinyl-acetylenes, become much less significant as the number of ethylenic bonds increases.

Another similarity between the conjugated polyenynes and the corresponding polyenes is observed in the straight line obtained when the squares of the wave-lengths of the main maxima of all of the polyenynes so far examined are plotted against the number of conjugations, the linearity of this relationship in the case of polyenes having already been established by Lewis and Calvin (*Chem. Reviews*, 1939, **25**, 273).

The subsidiary maxima at shorter wave-lengths observed with the polyenyne glycols (Figs. 2 and 3) are characteristic of polyenes, although these so-called " vorbanden " are not always recorded in the literature. Lewis and Calvin (*loc. cit.*) postulate that the ratio (R) of the wave-length of the subsidiary maximum to that of the main maximum should increase with increasing conjugation towards a maximum of 2. This was observed by them to be the case for all polyenes for which figures were available, and it also holds good for the polyenyne glycols (R = 1·2, 1·45, and 1·7 when n = 3, 5, and 7, respectively).

Experimental.

Tetradeca-2 : 4 : 10 : 12-tetraen-7-yn-6 : 9-diol (II; n = 2).—Pure dry acetylene was passed into an ethereal solution of ethylmagnesium bromide (from magnesium, 6 g.) at 20° during 24 hours, dry ether being added at intervals to maintain a constant volume of about 750 c.c. The acetylene was then replaced by nitrogen, and a solution of freshly distilled sorbaldehyde (22 g.) in dry ether (30 c.c.) was added during 30 minutes, accompanied by vigorous stirring which was continued for a further 2 hours. The Grignard complex was decomposed by treatment with a solution of ammonium nitrate (80 g.) in water, the aqueous phase was extracted several times with ether and, after the combined ethereal extracts had been washed consecutively with very dilute sulphuric acid and sodium bicarbonate solution and dried, the solvent was removed under diminished pressure. The residual pale brown viscous liquid was treated with dry benzene (15 c.c.), and, on standing at 0° for 24 hours, the glycol crystallised. The solid was repeatedly washed on the filter with small quantities of cold benzene, and crystallisation from benzene–light petroleum (b. p. 40—60°) and finally from *cyclo*hexane gave the *diol* (II; n = 2) (12 g.) as colourless prismatic needles, m. p. 95—102° (Found: C, 76·8; H, 8·15. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). *Active hydrogen* (Zerewitinoff): The glycol (128 mg.) gave 27·9 c.c. of methane at 21°/743 mm., equivalent to 1·95 active hydrogen atoms per mol. With a solution of antimony trichloride in chloroform the glycol gave a black precipitate.

Octadeca-2 : 4 : 6 : 12 : 14 : 16-hexaen-9-yn-8 : 11-diol (II; n = 3).—To a vigorously stirred suspension of acetylenyldimagnesium bromide (from magnesium, 6 g.) in ether, a solution of freshly distilled octatrienal (31 g.) in dry ether (40 c.c.) was added during ½ hour. Stirring, decomposition, and isolation were then carried out as previously described. In this case much ether had to be employed owing to the low solubility of the glycol in this solvent. The black syrup obtained after removal of the solvent was kept in contact with dry ether (50 c.c.) at 0° for 24 hours, and the crystalline glycol so obtained was filtered off and washed with several small portions of cold ether. A further quantity was obtained by repeating the treatment on the mother-liquors. Crystallisation from chloroform gave the *diol* (II; n = 3) (7 g.) as a mat of colourless needles, m. p. 154° (Found: C, 79·5, 79·7; H, 8·2, 8·15. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%). *Active hydrogen* (Zerewitinoff): The glycol (75 mg.) gave 13·1 c.c. of methane at 21°/763 mm. (1·95 active hydrogen atoms per mol.). With a solution of antimony trichloride in chloroform the glycol gave an immediate blue-green colour.

Tetradeca-3 : 5 : 9 : 11-tetraen-7-yn-2 : 13-diol (III; n = 2).—A solution of the diol (II; n = 2) (2 g.) in ether (10 c.c.) was shaken for 24 hours with sulphuric acid (20 c.c.; 5% w/v) at 20° under nitrogen. A yellow solid remained on evaporation of the washed and dried ethereal solution, and after being washed with small quantities of benzene and recrystallised under nitrogen from carbon tetrachloride, this yielded the *diol* (III; n = 2) (500 mg.) as plates, m. p. 115—116° (sealed tube) to an orange liquid (Found: C, 77·2; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). *Active hydrogen* (Zerewitinoff): The glycol (81 mg.) evolved 17·4 c.c. of methane at 22°/777 mm. (1·95 active hydrogen atoms per mol.). With a solution of antimony trichloride in chloroform, the glycol gave an immediate deep blue-violet colour, and a black precipitate slowly appeared; with anhydrous formic acid it slowly gave a greenish-blue coloration.

Decane-1 : 10-dicarboxylic Acid.—A solution of the above glycol (200 mg.) in methyl alcohol (15 c.c.) was shaken with hydrogen in the presence of platinic oxide (10 mg.) until absorption was complete. The crude tetradecane-2 : 13-diol obtained on removal of catalyst and solvent was shaken for 48 hours at 20° with sodium hypobromite solution (10 c.c.; 15%). The solid precipitated on acidification of the reaction mixture was crystallised from water, yielding decane-1 : 10-dicarboxylic acid, m. p. 126°, undepressed on admixture with an authentic specimen.

Octadeca-3 : 5 : 7 : 11 : 13 : 15-hexaen-9-yn-2 : 17-diol (III; n = 3).—A solution of the diol (II; n = 3) (4 g.) in alcohol or acetone was treated with sulphuric acid (10 c.c.; 10% w/v) and sufficient solvent was added to give a clear solution which was then set aside at 20° for 24 hours, by which time it had become deep yellow. After addition of an equal volume of water, the precipitated glycol was isolated by means of ether. Crystallisation of the product from benzene, under nitrogen, gave the *diol* (III; n = 3) (3·2 g.) as lemon-yellow needles, sinters 145°, m. p. 149° (sealed tube) to an orange liquid (Found: C, 80·0; H, 8·55. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%). *Active hydrogen* (Zerewitinoff): The glycol (102 mg.) evolved 17·3 c.c. of methane at 18°/768 mm. (1·95 active hydrogen atoms per mol.). With a solution of antimony trichloride in chloroform the glycol gave an immediate deep blue-violet colour. With anhydrous formic acid it gave an immediate brilliant green colour.

Tetradecane-1 : 14-dicarboxylic Acid (*Thapsic Acid*).—A solution of the above glycol (200 mg.) in methyl alcohol (15 c.c.) was shaken with hydrogen and platinic oxide (10 mg.) until absorption ceased. After removal of the catalyst and solvent, the crude octadecane-2 : 17-diol was finely powdered, and shaken with sodium hypobromite solution (10 c.c.; 15%) for 48 hours at 20°. Acidification with concentrated hydrochloric acid gave a solid which, after crystallisation from ethyl acetate, had m. p. 125—126° (Schmid and Kemeny, *Monatsh.*, 1935, **66**, 4, give m. p. 126° for thapsic acid).

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50. *Studies in the Polyene Series. Part XIV. Anionotropic Rearrangements of the Carbinols obtained from Condensation of Crotonaldehyde with both Vinyl- and 2-Methylvinyl-acetylene.*

By I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon.

Condensations of crotonaldehyde with both vinylacetylene and 2-methylvinylacetylene by either the Grignard or the sodium in liquid ammonia method are described. The propenylcarbinols undergo the expected anionotropic rearrangements (I ⟶ II) on shaking with 5% sulphuric acid.

In Part X (Heilbron, Johnson, Jones, and Raphael, J., 1943, 265) the preparation of 7-methylnona-2 : 7-dien-5-yn-4-ol (I; $R_1 = R_2 = Me$) from crotonaldehyde and 1 : 2-dimethylvinylacetylene, and its anionotropic rearrangement to 7-methylnona-3 : 7-dien-5-yn-2-ol (II; $R_1 = R_2 = Me$) in the presence of acids, were described. In spite of the statement by Carothers and Jacobson (*J. Amer. Chem. Soc.*, 1933, **55**, 1097) that unsaturated aldehydes and ketones are usually resinified completely by the sodio-derivative of vinylacetylene, attempts to condense crotonaldehyde with vinylacetylene itself appeared to offer promise of success. The conditions employed by the above authors, *viz.*, addition of sodamide to a solution of the aldehyde and vinylacetylene in dry ether, were such as to admit of extensive self-condensation of the crotonaldehyde, a reaction which can be suppressed almost entirely when this aldehyde is condensed with sodium acetylide in liquid ammonia (Jones and McCombie, J., 1942, 733). Also, there seems little reason why normal condensation should not occur by the Grignard method, and in a patent (Carothers and Berchet, U.S.P., 1,963,935) enumerating numerous reactions with vinylacetylenylmagnesium halides, crotonaldehyde is mentioned amongst many other aldehydes and ketones, but no details of either the condensation or the product obtained are given.

By the interaction of vinylacetylenylmagnesium bromide and crotonaldehyde, *octa*-2 : 7-*dien*-5-*yn*-4-*ol* (I; $R_1 = R_2 = H$) (*α-naphthylurethane*) was isolated in 35% yield, and a slightly lower yield was obtained by employing sodio-vinylacetylene in liquid ammonia. Similarly, from 2-methylvinylacetylene 7-*methylocta*-2 : 7-*dien*-5-*yn*-4-*ol* (I; $R_1 = Me$; $R_2 = H$) (*α-naphthylurethane*) was produced in 50 and 42% yields by the Grignard and the liquid ammonia method, respectively. On shaking with 5% sulphuric acid the carbinols were smoothly isomerised * into *octa*-3 : 7-*dien*-5-*yn*-2-*ol* (II; $R_1 = R_2 = H$) and 7-*methylocta*-3 : 7-*dien*-5-*yn*-2-*ol* (II; $R_1 = Me$; $R_2 = H$) (*α-naphthylurethane*) respectively, the constitution of the former being proved by hydrogenation and subsequent oxidation of the crude saturated carbinol to methyl hexyl ketone. Hydrogenation of the methylvinylacetylene product (II; $R_1 = Me$; $R_2 = H$) gave 7-*methyloctan*-2-*ol* (*α-naphthylurethane*), oxidised to 7-*methyloctan*-2-*one* (*semicarbazone*).

$$CH_3{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}C{\vdots}C{\cdot}CR_1{:}CHR_2 \quad (I.)$$
$$CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}C{\vdots}C{\cdot}CR_1{:}CHR_2 \quad (II.)$$

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{infl.}$, A.	$\varepsilon_{infl.}$
7-Methylnona-2 : 7-dien-5-yn-4-ol (I; $R_1 = R_2 = Me$) *	2250	15,500	2290	15,000
Octa-2 : 7-dien-5-yn-4-ol (I; $R_1 = R_2 = H$)	2240	15,000	2330	11,000
7-Methylocta-2 : 7-dien-5-yn-4-ol (I; $R_1 = Me$; $R_2 = H$)	2250	14,500	2300	12,000
7-Methylnona-3 : 7-dien-5-yn-2-ol (II; $R_1 = R_2 = Me$) *	2635	16,500	2690	15,500
Octa-3 : 7-dien-5-yn-2-ol (II; $R_1 = R_2 = H$)	2585	17,000	2450	13,500
			2700	15,500
7-Methylocta-3 : 7-dien-5-yn-2-ol (II; $R_1 = Me$; $R_2 = H$)	2585	17,000	2680	13,500

* Heilbron, Johnson, Jones, and Raphael, *loc. cit.*

The absorption spectra of the conjugated vinylacetylenyl- and divinylacetylenyl-carbinols (table; alcoholic solutions) described in this paper are closely analogous, in both location and intensity of the maxima and inflexions, to those previously recorded (Parts VIII—XI, J., 1943, 261—270).

Experimental.

Octa-2 : 7-*dien*-5-*yn*-4-*ol* (I; $R_1 = R_2 = H$).—(*a*) A solution of vinylacetylene [23 g. (crude), made according to Schmitz and Schumacher, *Z. Electrochem.*, 1939, **45**, 503] in ether (120 c.c.) was added during one hour to a stirred ethereal solution of ethylmagnesium bromide (from 7 g. of magnesium) contained in a three-necked flask fitted with a double-surface condenser containing solid carbon dioxide. The mixture was kept at 20° for 2 hours after completion of the addition, and was then treated dropwise with a solution of crotonaldehyde (19 g.) in ether (20 c.c.). It was stirred for a further 4 hours and then set aside over-night. The Grignard complex was decomposed with ice and ammonium chloride (50 g.), and the product isolated by means of ether. This gave *octa*-2 : 7-*dien*-5-*yn*-4-*ol* (12 g.) as a practically colourless liquid, which darkens on standing, b. p. 72—73°/3·5 mm., $n_D^{19°}$ 1·5076 (Found: C, 78·7; H, 8·5. $C_8H_{10}O$ requires C, 78·65; H, 8·25%). *Active hydrogen* (Zerewitinoff): The carbinol (118 mg.) evolved 24 c.c. of methane at 19°/762 mm., corresponding to 1·05 active hydrogen atoms per mol. The *α-naphthylurethane* separated from light petroleum (b. p. 60—80°) or aqueous acetone in needles, m. p. 95—96° (Found: C, 78·65; H, 6·2. $C_{19}H_{17}O_2N$ requires C, 78·3; H, 5·9%).

(*b*) Sodium (13·5 g.) and a solution of vinylacetylene (43 g.: crude) in ether (200 c.c.) were gradually added to stirred liquid ammonia (1500 c.c.) in such a manner that the solution became colourless before each fresh addition of sodium was made. The operation took approximately 2 hours, after which the solution was treated with crotonaldehyde (42 g.) in ether (50 c.c.) during 45 minutes. The mixture was stirred for a further 2½ hours, ammonium chloride (33 g.) added, and

* Patent protection pending.

the ammonia allowed to evaporate off overnight in a stream of nitrogen. Isolation by means of ether gave octa-2 : 7-dien-5-yn-4-ol (24 g.), b. p. 77—79°/4·5 mm., $n_D^{19°}$ 1·5063.

Octa-3 : 7-dien-5-yn-2-ol (II; $R_1 = R_2 = H$).—A mixture of the above carbinol (8·5 g.) and sulphuric acid (50 c.c.; 5% w/v) was shaken under nitrogen at 20° for 24 hours. The upper layer was separated with ether and gave *octa-3 : 7-dien-5-yn-2-ol* (6 g.) as an almost colourless oil, b. p. about 78°/4 mm., $n_D^{17°}$ 1·5388 (Found : C, 78·5; H, 8·1. $C_8H_{10}O$ requires C, 78·65; H, 8·25%). Much dinaphthylurea was formed on treating the carbinol with α-naphthyl *iso*cyanate at 20°, and no crystalline α-naphthylurethane could be obtained.

Methyl Hexyl Ketone.—A solution of octa-3 : 7-dien-5-yn-2-ol (3·4 g.) in ethyl acetate (35 c.c.) was shaken with hydrogen in presence of platinic oxide (100 mg.) until absorption was complete. The carbinol obtained after removal of catalyst and solvent was oxidised with chromic acid in sulphuric acid, giving methyl hexyl ketone, b. p. 56—59°/11 mm., $n_D^{20°}$ 1·4163 (Brühl, *Annalen*, 1880, **203**, 29, gives b. p. 173°/753 mm., $n_D^{20°}$ 1·4161). The semicarbazone had m. p. 122—123° (Bouveault and Locquin, *Bull. Soc. chim.*, 1904, **31**, 1157, give m. p. 122°) and gave no depression on admixture with an authentic specimen.

7-Methylocta-2 : 7-dien-5-yn-4-ol (I; $R_1 = Me$; $R_2 = H$).—(*a*) 2-Methylvinylacetylene (41 g.; Thompson, Milas, and Rovno, *J. Amer. Chem. Soc.*, 1941, **63**, 752) was caused to react with sodium (12 g.) in liquid ammonia (750 c.c.) as previously described, and the solution of the sodio-derivative was treated with crotonaldehyde (43 g.) in ether (50 c.c.) and stirred for 3 hours. Isolation of the product in the usual manner gave *7-methylocta-2 : 7-dien-5-yn-4-ol* (30 g.) as a pale yellow liquid, b. p. 62—68°/3 mm., $n_D^{17°}$ 1·5027 (Found : C, 79·4; H, 9·0. $C_9H_{12}O$ requires C, 79·35; H, 8·9%). *Active hydrogen* (Zerewitinoff) : The carbinol (95 mg.) gave 16·5 c.c. of methane at 19°/755 mm. (1·0 active hydrogen atom per mol.). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 99° (Found : C, 78·4; H, 6·2. $C_{20}H_{19}O_2N$ requires C, 78·65; H, 6·25%).

(*b*) A Grignard condensation between 2-methylvinylacetylene (67 g.) and crotonaldehyde (63 g.) effected as described above (ethylmagnesium bromide from magnesium, 22 g.) gave 7-methylocta-2 : 7-dien-5-yn-4-ol (58 g.), b. p. *ca.* 75°/3 mm., $n_D^{17°}$ 1·5015.

7-Methylocta-3 : 7-dien-5-yn-2-ol (II; $R_1 = Me$; $R_2 = H$).—A mixture of 7-methylocta-2 : 7-dien-5-yn-4-ol (20 g.) and sulphuric acid (100 c.c.; 5% w/v) was shaken at 20° for 24 hours in nitrogen. Isolation by means of ether gave the *carbinol* (II; $R_1 = Me$; $R_2 = H$) (16·4 g.) as a very pale yellow liquid, b. p. 75—78°/2 mm., 27° (bath temp.)/10^{-4} mm., $n_D^{17°}$ 1·5265 (Found : C, 79·45; H, 8·9. $C_9H_{12}O$ requires C, 79·35; H, 8·9%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 80—100°) in small needles, m. p. 89° (Found : C, 78·85; H, 6·35. $C_{20}H_{19}O_2N$ requires C, 78·65; H, 6·25%).

7-Methyloctan-2-ol and *7-Methyloctan-2-one.*—A solution of 7-methylocta-3 : 7-dien-5-yn-2-ol (10 g.) in ethyl acetate (35 c.c.) was shaken with hydrogen in the presence of platinic oxide (200 mg.) until absorption was complete. The residue obtained after removal of catalyst and solvent was twice distilled, yielding *7-methyloctan-2-ol* (6·3 g.), b. p. 57°/3 mm., $n_D^{20°}$ 1·4309 (Found : C, 74·25; H, 13·45. $C_9H_{20}O$ requires C, 74·9; H, 13·95%). The *α-naphthylurethane* separated from light petroleum (b. p. 40—60°) in needles, m. p. 75° (Found : C, 76·95; H, 8·6. $C_{20}H_{27}O_2N$ requires C, 76·65; H, 8·7%). Oxidation of the carbinol with chromic acid in sulphuric acid gave *7-methyloctan-2-one*, b. p. 78°/17 mm., $n_D^{15°}$ 1·4228 (Found : C, 76·25; H, 12·85. $C_9H_{18}O$ requires C, 76·0; H, 12·75%). The *semicarbazone* crystallised from aqueous alcohol or benzene–light petroleum (b. p. 100—120°) in prismatic needles, m. p. 132—133° (Found : C, 60·65; H, 10·45; N, 21·3. $C_{10}H_{21}ON_3$ requires C, 60·25; H, 10·65; N, 21·1%).

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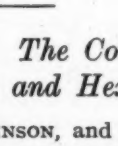
51. *Studies in the Polyene Series. Part XV. The Condensation of Carbonyl Compounds with Propenylethynylcarbinol and Hex-3-en-5-yn-2-ol.*

By J. CYMERMAN, I. M. HEILBRON, A. W. JOHNSON, and E. R. H. JONES.

Propenylethynylcarbinol (III) has been condensed by the Grignard method with benzophenone, butaldehyde, benzaldehyde, and crotonaldehyde, the acetylenyl glycols (V)—(VIII) being obtained in yields ranging from 40 to 55%. In a similar manner the glycols (IX)—(XIII) and (XV) were isolated from condensation between hex-3-en-5-yn-2-ol (IV) and the appropriate aldehydes and ketones. By anionotropic rearrangement in the presence of acids the glycol (VI) has been converted into its isomer (IX), and both (VIII) and (XIII) have been isomerised to the symmetrical glycol (XIV). The products derived from hex-3-en-5-yn-2-ol, with the exception of (XV) which has been shown to dissociate into benzophenone on ultra-violet irradiation, exhibit light-absorption characteristics consistent with the presence of the conjugated vinylacetylene chromophore in their molecules.

ONE of the routes outlined in Part V (Heilbron, Johnson, Jones, and Spinks, J., 1942, 727) for the synthesis of polyenes of the vitamin A type involved condensations between substituted ethynylcarbinols, particularly vinylacetylenylcarbinols such as 3-methylpent-2-en-4-yn-1-ol (I), and carbonyl compounds, particularly

(I.) $HC{:}C{\cdot}CMe{:}CH{\cdot}CH_2{\cdot}OH$



$CH_2{\cdot}CH{:}CMe{\cdot}CHO$ (II.)

(III.) $CH_2{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}C{:}CH$

$CH_3{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}C{:}CH$ (IV.)

unsaturated aldehydes such as 3-(2′ : 6′ : 6′-trimethyl*cyclo*hexenyl)-1-methylcrotonaldehyde (II). As a preliminary, the condensation of the readily available acetylenic alcohols propenylethynylcarbinol (III) and hex-3-en-5-yn-2-ol (IV) (Jones and McCombie, J., 1942, 733; 1943, 261) with simple saturated and unsaturated aldehydes and ketones has been examined.

Marvel and his co-workers (*inter alia*, *J. Org. Chem.*, 1942, **7**, 93; *J. Amer. Chem. Soc.*, 1939, **61**, 2006), employing the Grignard method, have provided innumerable examples of condensations between simple

ethynylcarbinols, *e.g.*, 1-ethynyl*cyclo*hexanol, and saturated ketones. The method involves the addition of one mole of the ethynylcarbinol to two moles of ethylmagnesium bromide whereby both active hydrogen atoms are replaced by MgBr groups. The carbonyl compound (1 mole) is then added and condensation ensues, producing, after decomposition of the Grignard complex in the usual manner, the acetylenyl glycols, either symmetrical or unsymmetrical, in good yields. For other examples of Grignard condensations, see Zalkind and Gverdtsiteli (*J. Gen. Chem. Russia*, **1939**, **9**, 855), who described the reaction of dimethylethynylcarbinol with *cyclo*pentanone, Zeile and Meyer (*Ber.*, **1942**, **75**, 356), and Losac'h (*Bull. Soc. chim.*, **1941**, **8**, 519). Condensing agents such as sodamide (Henecka, *Chem. Abstracts*, **1937**, **31**, 2592), potassium *tert.*-butoxide (Burkhardt and Hindley, J., 1938, 989), potassium hydroxide (Babajan, *J. Gen. Chem. Russia*, **1940**, **10**, 480, 1177), and copper and similar acetylides (General Aniline and Film Corp., U.S.P. 2,238,471) are applicable in certain simple cases. The only recorded employment of ethylenic ethynylcarbinols in such reactions is that by Teterin and Ivanov (*J. Gen. Chem. Russia*, **1937**, **7**, 1629), who prepared 1 : 1-diphenylhept-5-en-2-yn-1 : 4-diol (V) from propenylethynylcarbinol (III) and benzophenone by the Grignard method. There is no mention in the literature of condensations between ethynylcarbinols and unsaturated carbonyl compounds. Similarly, condensations involving conjugated vinylacetylenylcarbinols such as (I) and (IV) have apparently never been attempted.

Repetition of Teterin and Ivanov's work (*loc. cit.*) gave the glycol (V), m. p. 131° (*lit.*, m. p. 124°), which contains two active hydrogen atoms as estimated by the Zerewitinoff method. In this respect all the glycols subsequently described in this paper behaved normally. Condensation between butaldehyde and propenylethynylcarbinol (III) by the Grignard method, which was used without exception for all the condensations herein described, furnished *dec-2-en-5-yn-4* : *7-diol* (VI) in 55% yield. The glycol was obtained as a viscous oil, which gave two *bisphenylurethanes* [m. p.'s 153° (decomp.) and 125°] probably derived from the two theoretically possible *dl*-forms of the glycol. When benzaldehyde reacted with (III) a 40% yield of *1-phenylhept-5-en-2-yn-1* : *4-diol* (VII) (m. p. 108°) was obtained, and in this case there was little evidence of the presence of stereoisomerides in the reaction mixture. A similar experiment employing crotonaldehyde gave a 40% yield of

$CPh_2(OH)\cdot C{:}C\cdot CH(OH)\cdot CH{:}CH\cdot CH_3$ (V.)
$CH_3\cdot CH_2\cdot CH_2\cdot CH(OH)\cdot C{:}C\cdot CH(OH)\cdot CH{:}CH\cdot CH_3$ (VI.)
$CHPh(OH)\cdot C{:}C\cdot CH(OH)\cdot CH{:}CH\cdot CH_3$ (VII.)
$CH_3\cdot CH{:}CH\cdot CH(OH)\cdot C{:}C\cdot CH(OH)\cdot CH{:}CH\cdot CH_3$ (VIII.)

mixed isomers of deca-2 : 8-dien-5-yn-4 : 7-diol (VIII), from which the pure crystalline glycol, m. p. 91°, was isolated (cf. Heilbron, Jones, and Raphael, J., 1943, 268; Dupont, *Ann. Chim.*, **1913**, **30**, 499).

When hex-3-en-5-yn-2-ol (IV), prepared by anionotropic rearrangement of propenylethynylcarbinol (III) with acids (Jones and McCombie, J., 1943, 261), was condensed with butaldehyde, a 45% yield of *dec-3-en-5-yn-2* : *7-diol* (IX) was obtained; this was also prepared by isomerisation of (VI) with either 2·5% or 10% sulphuric acid. Replacement of the acetylenic hydrogen atom of propenylethynylcarbinol by a propylcarbinol group thus appears to have no profound effect on the ease of anionotropic rearrangement in systems such as $\cdot C{:}C\cdot CH(OH)\cdot CH{:}CH\cdot CH_3$. Comparison of the products obtained by the two methods could only be made by means of refractive index and light-absorption measurements since no crystalline derivatives were obtainable from either specimen of glycol. These are certainly mixtures of stereoisomerides and it might be expected that, since the ethylenic linkage in these compounds has been involved in the isomerisation, geometrical isomerides of the two possible *dl*-forms would be encountered.

By similar condensations, benzaldehyde was converted into *1-phenylhept-4-en-2-yn-1* : *6-diol* (X) in 60% yield, anisaldehyde gave a 30% yield of the p-*methoxy-analogue* (XI), m. p. 19—20°, and methyl ethyl ketone yielded 70% of the theoretical amount of *3-methylnon-6-en-4-yn-3* : *8-diol* (XII). From crotonaldehyde a 50% yield of *deca-3* : *8-dien-5-yn-2* : *7-diol* (XIII) was obtained, and on shaking this glycol with 4% sulphuric acid

$CH_3\cdot CH_2\cdot CH_2\cdot CH(OH)\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (IX.)
$CHPh(OH)\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (X.)
$(p)\text{-}OMe\cdot C_6H_4\cdot CH(OH)\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (XI.)
$CH_3\cdot CH_2\cdot C(OH)Me\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (XII.)
$CH_3\cdot CH{:}CH\cdot CH(OH)\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (XIII.)
$CH_3\cdot CH(OH)\cdot CH{:}CH\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (XIV.)
$CPh_2(OH)\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3$ (XV.)

it was converted into deca-3 : 7-dien-5-yn-2 : 9-diol (XIV), previously prepared by a dual anionotropic rearrangement of the acetylenyl glycol from crotonaldehyde (Heilbron, Jones, and Raphael, J., 1943, 268). 1 : 1-*Diphenylhept-4-en-2-yn-1* : *6-diol* (XV) was isolated (50% yield) from the condensation of benzophenone with (IV), but attempts to obtain it by isomerisation of (V), even with 25% sulphuric acid, gave only unchanged material. However, it cannot be stated definitely that the diphenylcarbinol group has a powerful deactivating effect on the mobility of the anionotropic system since it appears likely that solubility factors would be of importance in this case. Experiments carried out in homogeneous media have so far proved inconclusive.

With the exception of the glycol (XV) derived from benzophenone, the products obtained from condensations with hex-3-en-5-yn-2-ol (IV) all exhibit light absorption (see table) characteristic of the conjugated vinylacetylene chromophore (Parts VIII—X), although inflexions were not observed in every case, attributable possibly to the presence of stereoisomerides.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{inf.}$, A.	$\varepsilon_{inf.}$
Hex-3-en-5-yn-2-ol [1] (IV)	2230	13,000	2300	9,500
Dec-3-en-5-yn-2 : 7-diol (IX)	2280	15,000	2380	11,500
1-Phenylhept-4-en-2-yn-1 : 6-diol (X)	2240	12,500	2350	11,500
1-(*p*-Methoxyphenyl)hept-4-en-2-yn-1 : 6-diol (XI)	2250	17,500	—	—
3-Methylnon-6-en-4-yn-3 : 8-diol (XII)	2285	12,500	2350	11,000
Deca-3 : 8-dien-5-yn-2 : 7-diol (XIII)	2280	13,000	—	—
1 : 1-Diphenylhept-4-en-2-yn-1 : 6-diol (XV)	2510	21,000	—	—
	3315	13,500	—	—
Benzophenone [2]	2520	20,000	—	—
	3300	160	—	—

[1] Jones and McCombie, J., 1943, 261. [2] Scheibe, *Ber.*, 1926, **59**, 2617.

The absorption spectrum of (XV) appeared to be distinctly anomalous, and, in fact, bore a resemblance to that of the parent ketone, benzophenone. It had been noted during the preparation of (XV) that much of the latter ketone was present in the product, but there was no doubt that the spectrographic and analytical samples were free from ketone. It was then ascertained from refractive-index measurements that some fission of the glycol took place during distillation even in a high vacuum, benzophenone distilling over first, followed by the glycol, the quantity of the latter decreasing progressively on repeated distillation. That a similar fission took place by the action of ultra-violet light during the light-absorption measurements was proved by irradiating a solution of the pure glycol in alcohol in a quartz cell with light from a mercury arc, whereupon benzophenone was readily detected in the solution by testing with 2 : 4-dinitrophenylhydrazine, the original solution failing to give any trace of the ketonic derivative.

The reversion of acetylenic carbinols into the constituent carbonyl compounds and acetylenes by the action of alkalis is well known and cases of cleavage on distillation have been recorded (Armour and Co., E.P. 529,794), but fission simply by ultra-violet irradiation does not appear to have been observed hitherto. In this case the effect of the two phenyl groups in weakening the carbon–carbon bond must be accentuated by the adjacent conjugated vinylacetylene group, since no decomposition of the unrearranged glycol (V) was observed.

Experimental.

(Absorption spectra were determined in alcoholic solutions.)

1 : 1-*Diphenylhept-5-en-2-yn-1* : 4-*diol* (V).—Propenylethynylcarbinol (24 g.) was added during 1 hour to an ethereal solution of ethylmagnesium bromide (from 12 g. of magnesium), and the mixture refluxed for 2 hours. After ice-cooling, a solution of benzophenone (45 g.) in ether was added dropwise, the mixture was set aside overnight, and finally refluxed for 1 hour. The Grignard complex was decomposed with ammonium chloride solution (ice), and isolation by the normal procedure yielded the glycol (43 g.), after crystallisation from benzene, as needles, m. p. 131° (Teterin and Ivanov, *loc. cit.*, give m. p. 124°) (Found : C, 81·5; H, 6·45. Calc. for $C_{19}H_{18}O_2$: C, 81·95; H, 6·5%). *Active hydrogen* (Zerewitinoff) : The glycol (98·5 mg.) evolved 18·7 c.c. of methane at 22°/750 mm., equivalent to 2·1 active hydrogen atoms per mol. *Light absorption* : Maximum 2210 A.; $\varepsilon = 12{,}500$. Inflexion, 2280 A.; $\varepsilon = 10{,}500$.

Dec-2-en-5-yn-4 : 7-*diol* (VI.)—By using the method employed above, butaldehyde (9 g.) was condensed with propenylethynylcarbinol (12·5 g.), giving *dec-2-en-5-yn-4* : 7-*diol* (12 g.) as a viscous liquid, b. p. 52° (bath temp.)/10^{-4} mm., $n_D^{16°}$ 1·4666 (Found : C, 71·1; H, 9·8. $C_{10}H_{16}O_2$ requires C, 71·35; H, 9·6%). *Active hydrogen* (Zerewitinoff) : The glycol (42·1 mg.) evolved 11·2 c.c. of methane at 18°/777 mm. (1·95 active hydrogen atoms per mol.). The glycol exhibited no absorption of appreciable intensity in the ultra-violet. Two *bisphenylurethanes* were obtained from the glycol by reaction with phenyl *iso*cyanate; the more insoluble form separated from methyl alcohol as needles, m. p. 125° (Found : N, 6·8. $C_{24}H_{26}O_4N_2$ requires N, 6·9%), and the other form crystallised from alcohol in rhombic plates, m. p. 153° (decomp.) (Found : N, 6·95%). Only one *bis-α-naphthylurethane* could be obtained in a pure condition. It separated from alcohol in needles, m. p. 194° (decomp.) (Found : N, 5·75. $C_{32}H_{30}O_4N_2$ requires N, 5·55%).

1-*Phenylhept-5-en-2-yn-1* : 4-*diol* (VII).—This was prepared by the general method from propenylethynylcarbinol (12 g.) and benzaldehyde (13 g.). Distillation of the crude glycol gave an oil (10·5 g.), b. p. 80—90° (bath temp.)/10^{-4} mm., which solidified, and when crystallised from benzene yielded 1-*phenylhept-5-en-2-yn-1* : 4-*diol* as prismatic needles, m. p. 108° (Found : C, 77·5; H, 6·9. $C_{13}H_{16}O_2$ requires C, 77·2; H, 7·0%). *Active hydrogen* (Zerewitinoff) : The glycol (100 mg.) evolved 25·3 c.c. of methane at 22°/762 mm. (2·1 active hydrogen atoms per mol.). *Light absorption* : Maximum, 2180 A.; $\varepsilon = 5000$. Inflexion, 2240 A.; $\varepsilon = 2000$.

Deca-2 : 8-*dien-5-yn-4* : 7-*diol* (VIII).—Condensation of propenylethynylcarbinol (12 g.) with crotonaldehyde (8·8 g.) gave the glycol (9 g.), b. p. 90—100° (bath temp.)/10^{-4} mm., which solidified on cooling and, when crystallised from carbon tetrachloride or benzene, formed needles, m. p. 91° (Dupont, *loc. cit.*, gives m. p. 90—92°). It gave no depression in m. p. on admixture with an authentic specimen prepared by Dupont's method and exhibited no light absorption of appreciable intensity in the ultra-violet.

Dec-3-en-5-yn-2 : 7-*diol* (IX).—(a) When prepared from hex-3-en-5-yn-2-ol (6 g.) and butaldehyde (4·5 g.) in the usual manner, *dec-3-en-5-yn-2* : 7-*diol* (4·5 g.) was isolated with b. p. 72° (bath temp.)/10^{-4} mm., $n_D^{16°}$ 1·5038 (Found : C, 70·9; H, 9·4. $C_{10}H_{18}O_2$ requires C, 71·35; H, 9·6%). *Active hydrogen* (Zerewitinoff) : The glycol (114 mg.) evolved 34·6 c.c. of methane at 22°/777 mm. (2·1 active hydrogen atoms per mol.). *Light absorption* : see table.

(b) A mixture of dec-2-en-5-yn-4 : 7-diol (1·5 g.) and sulphuric acid (60 c.c.; 2·5% w/v) was shaken at 20° for 15 hours. Isolation of the product with ether gave dec-3-en-5-yn-2 : 7-diol (1·2 g.), b. p. 75° (bath temp.)/10^{-4} mm., $n_D^{15°}$ 1·5032. *Light absorption* : Maximum, 2275 A; $\varepsilon = 15{,}000$. Inflexion, 2360 A.; $\varepsilon = 12{,}500$. Shaking with 10% sulphuric acid for the same time gave a glycol with identical properties.

1-*Phenylhept-4-en-2-yn-1* : 6-*diol* (X).—Prepared by condensation of hex-3-en-5-yn-2-ol (6 g.) with benzaldehyde (6 g.), this *diol* (7·5 g.) was obtained after 3 distillations as a pale yellow oil, b. p. 78° (bath temp.)/10^{-4} mm., $n_D^{17°}$ 1·5694 (Found : C, 77·1; H, 7·3. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%). *Active hydrogen* (Zerewitinoff) : The glycol (112 mg.) evolved 26·45 c.c. of methane at 20°/763 mm. (2·0 active hydrogen atoms per mol.).

1-(p-*Methoxyphenyl*)*hept-4-en-2-yn-1* : 6-*diol* (XI.)—Reaction between hex-3-en-5-yn-2-ol (6 g.) and anisaldehyde (8·5 g.) yielded a crude product (12 g.), the non-aldehydic portion of which, separated by means of Girard reagent P, yielded the *diol* (XI) (4 g.), b. p. 60° (bath temp.)/10^{-4} mm., $n_D^{16°}$ 1·5424. On standing at 0° it solidified to needles, m. p.

19—20° (Found: C, 72·3; H, 7·45. $C_{14}H_{16}O_3$ requires C, 72·35; H, 6·95%). *Active hydrogen* (Zerewitinoff): The glycol (94 mg.) evolved 20·0 c.c. of methane at 20°/737 mm. (2·0 active hydrogen atoms per mol.).

3-*Methylnon*-6-*en*-4-*yn*-3 : 8-*diol* (XII).—Condensation between hex-3-en-5-yn-2-ol (6 g.) and methyl ethyl ketone (4 g.) yielded the *glycol* as a viscous oil (6·5 g.), b. p. 63° (bath temp.)/10^{-4} mm., $n_D^{17°}$ 1·4989 (Found: C, 71·7; H, 9·75. $C_{10}H_{18}O_2$ requires C, 71·35; H, 9·6%). *Active hydrogen* (Zerewitinoff): The glycol (79 mg.) evolved 20·1 c.c. of methane at 21°/753 mm. (1·9 active hydrogen atoms per mol.).

Deca-3 : 8-*dien*-5-*yn*-2 : 7-*diol* (XIII).—Condensation between hex-3-en-5-yn-2-ol (6 g.) and crotonaldehyde (4 g.) yielded the *diol* (XIII) (4·8 g.) as a pale yellow oil, b. p. 75° (bath temp.)/10^{-4} mm., $n_D^{19°}$ 1·5309 (Found: C, 72·3; H, 8·75. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%). *Active hydrogen* (Zerewitinoff): The glycol (121 mg.) gave 34·15 c.c. of methane at 16°/755 mm. (2·0 active hydrogen atoms per mol.).

Deca-3 : 7-*dien*-5-*yn*-2 : 9-*diol* (XIV).—A mixture of deca-3 : 8-dien-5-yn-2 : 7-diol (200 mg.) and sulphuric acid (20 c.c.; 4% w/v) was shaken under nitrogen for 25 hours at 20°. Isolation by means of ether yielded the diol (XIV) (100 mg.) as a pale yellow viscous oil, b. p. 110—115° (bath temp.)/10^{-4} mm., $n_D^{21°}$ 1·5501 (Heilbron, Jones, and Raphael, *loc. cit.*, give $n_D^{21°}$ 1·5511). *Light absorption:* Maxima, 2660 and 2790 A.; $\varepsilon = 17{,}500$ and 15,000, respectively.

1 : 1-*Diphenylhept*-4-*en*-2-*yn*-1 : 6-*diol* (XV).—Prepared as described above from hex-3-en-5-yn-2-ol (12 g.) and benzophenone (21 g.), after two distillations this *diol* (12 g.) was obtained as a pale yellow viscous oil, b. p. 85° (bath temp.)/10^{-4} mm., $n_D^{17°}$ 1·6468 (Found: C, 82·15; H, 6·45. $C_{19}H_{18}O_2$ requires C, 81·95; H, 6·5%). *Active hydrogen* (Zerewitinoff): The glycol (109·5 mg.) evolved 19·5 c.c. of methane at 20°/763 mm. (2·05 active hydrogen atoms per mol.). A portion of a solution of the glycol (20 mg.) in alcohol (4 c.c.) gave no positive ketonic reaction when treated with an alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate. After irradiation in a quartz cell with light from a mercury vapour lamp for 10 minutes, similar treatment gave the 2 : 4-dinitrophenylhydrazone of benzophenone, which crystallised from acetic acid in red crystals, m. p. 234° (decomp.), undepressed on admixture with an authentic specimen.

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52. *Studies in the Polyene Series. Part XVI. The Condensation of αβ-Unsaturated Ketones with 1-Hexyne.*

By J. Cymerman, I. M. Heilbron, and E. R. H. Jones.

Condensations between hexynylmagnesium bromide and methyl vinyl ketone, ethylideneacetone, and mesityl oxide give 60% yields of the expected tertiary carbinols (I). The experimental conditions are somewhat critical, as rearrangement and dehydration may ensue, but low reaction temperatures and low concentrations of reactants in general favour formation of the normal products. Anionotropic rearrangements of the tertiary carbinols (I) to the conjugated vinylacetylenylcarbinols (II) are considerably more facile than those of closely related secondary carbinols and an obvious explanation is suggested. The isomerisation products (II) all exhibit the anticipated light-absorption characteristic of the vinylacetylene chromophore, and their structures have been rigidly proved by complete hydrogenation.

Although the literature abounds with references to the condensation of carbonyl compounds with acetylene, very few condensations involving αβ-unsaturated ketones have been described. We have found that such condensations are by no means easy to effect, the yields obtainable by the standard methods being usually poor and often negligible. Work on this problem is still proceeding; however, considerable progress has been made and the results will be published in due course. Since we were at least equally interested (J., 1942, 727) in the interaction of substituted acetylenes with αβ-unsaturated ketones, and since rather more favourable indications were obtained from a perusal of the literature, we have studied the condensation of a substituted acetylene, 1-hexyne, with three simple unsaturated ketones.

The most satisfactory method of effecting condensations with alkylacetylenes is by means of their Grignard complexes. Reactions between Grignard reagents and αβ-unsaturated ketones, however, may take place by either 1 : 2- or 1 : 4-addition (Kohler *et al.*, *Amer. Chem. J.*, 1909, **42**, 375; 1907, **38**, 5; 1904, **31**, 642), but with hexynylmagnesium bromide and the three simple ketones chosen for this study, no indication of the formation of 1 : 4-addition products was ever obtained.

As far as we are aware, Grignard reactions have not hitherto been performed with the simplest αβ-unsaturated ketone, methyl vinyl ketone. [While this paper was being prepared for publication, Smith and Sprung (*J. Amer. Chem. Soc.*, 1943, **65**, 1276) reported failure to make it react with laurylmagnesium bromide, owing to polymerisation of the ketone.] Nevertheless, when it was allowed to react with hexynylmagnesium bromide at room temperature, 3-*methylnon*-1-*en*-4-*yn*-3-*ol* (I; $R_1 = R_2 = H$) was obtained without difficulty in 55% yield. (Smith and Sprung may have carried out their experiments in boiling ethereal solutions.) As evidence that normal 1 : 2-addition had occurred, the following facts may be cited. The product contained one active hydrogen atom (Zerewitinoff), it exhibited no appreciable absorption in the ultra-violet, and failed to react even after long standing with phenyl or α-naphthyl *iso*cyanate. Since the tertiary carbinol obtainable on complete hydrogenation would not readily be characterised, such evidence for the structure assigned was not sought, but it is to be noted that the facile anionotropic rearrangement (described later) to a product whose constitution has been rigidly proved provides ample confirmation of the correctness of the formulation of the original condensation product.

A similar condensation with ethylideneacetone gave 4-*methyldec*-2-*en*-5-*yn*-4-*ol* (I; $R_1 = H$; $R_2 = Me$) in 55% yield, this carbinol possessing properties closely akin to those of the methyl vinyl ketone product. The greater accessibility of the parent ketone permitted a more detailed study of this reaction from which

valuable information was gained. When the condensation between the hexynylmagnesium bromide and the αβ-unsaturated ketone was carried out in boiling ethereal solution, the product obtained corresponded closely

$$CH_3\cdot[CH_2]_3\cdot C{:}C\cdot C(OH)Me\cdot CH{:}CR_1R_2 \quad (I.)$$
$$CH_3\cdot[CH_2]_3\cdot C{:}C\cdot CMe{:}CH\cdot C(OH)R_1R_2 \quad (II.)$$
$$CH_3\cdot[CH_2]_3\cdot C{:}C\cdot CMe{:}CH\cdot CH{:}CH_2 \quad (III.)$$

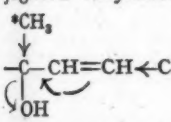
in its constants to that of the isomeric carbinol (II; $R_1 = H$; $R_2 = Me$) which, as will be seen later, is normally produced by the action of acids on the original condensation product. It would thus appear that at quite moderate temperatures the –OMgBr group participates in an anionotropic rearrangement. When hexynylmagnesium iodide was employed in place of the bromide in an experiment in which the reaction mixture was refluxed for some hours, a mixture consisting entirely of hydrocarbons (no active hydrogen) was obtained. One fraction, which showed intense and complex light absorption (maxima at 2360, 2620, and an inflexion at 2740 A.; $E^{1\%}_{1\,cm.}$ 720, 480, and 370, respectively) obviously contained an appreciable quantity of a triply unsaturated hydrocarbon such as (III). It is obvious that the intermediate organometallic complexes (particularly the magnesium iodide) in these Grignard condensations are somewhat labile, and in this connection it has also been observed that normal condensation products can only be isolated provided the reactions are effected in moderately dilute solutions. Jacquemain (*Compt. rend.*, **1934**, **198**, 483) found that the use of alkylmagnesium iodides in Grignard reactions with mesityl oxide resulted in extensive dehydration of the tertiary carbinols.

The nature of the product isolated from condensations between mesityl oxide and hexynylmagnesium bromide was even more dependent upon the experimental conditions. In warm concentrated solutions the product consisted entirely of hydrocarbon, whereas in cold dilute solutions, a 66% yield of 2 : 4-*dimethyldec*-2-*en*-5-*yn*-4-*ol* (I; $R_1 = R_2 = Me$) was readily achieved, the carbinol exhibiting properties in accord with the formulation given. This ease of dehydration may explain why Nazarov and Elizarova (*Chem. Abstracts*, 1942, **36**, 742) obtained only a hydrocarbon on condensing mesityl oxide with vinylacetylenylmagnesium bromide.

The rearrangement in the presence of acids of numerous acetylenic carbinols and glycols derived from unsaturated aldehydes has been thoroughly described in the preceding papers in this series (Parts VIII—XV),

$$CH_3\cdot[CH_2]_3\cdot C{:}C\cdot CH(OH)\cdot CH{:}CH\cdot CH_3 \quad (IV.)$$
$$CH_3\cdot[CH_2]_3\cdot C{:}C\cdot CH{:}CH\cdot CH(OH)\cdot CH_3 \quad (V.)$$

the condensation product (IV) between 1-hexyne and crotonaldehyde, for example, isomerising to the conjugated vinylacetylenylcarbinol (V) on shaking with 25% sulphuric acid for 24 hours. In the cases of the carbinols (I) derived from hexyne and αβ-unsaturated ketones, the rearrangement is much more facile, shaking with 0·5% sulphuric acid for 3—5 hours sufficing to give practically quantitative yields of the isomeric carbinols (II). Solubility differences between (IV) and (I; $R_1 = H$; $R_2 = Me$) can only be of a low order, and the increased mobility of the anionotropic system must be occasioned mainly by the inductive effect of the additional methyl group (*, in inset), which would naturally tend to facilitate the separation of the hydroxylic anion.



Isomerisation of the carbinol (I; $R_1 = R_2 = H$) from methyl vinyl ketone by shaking for 4 hours with 0·5% sulphuric acid gave an excellent yield of 3-*methylnon*-2-*en*-4-*yn*-1-*ol* (II; $R_1 = R_2 = H$) which, being a primary alcohol, formed an *α-naphthylurethane* very readily. Its constitution was proved by hydrogenation to 3-methylnonan-1-ol (*α-naphthylurethane*) which was oxidised to 2-*n*-hexylbutyric acid. Since no solid derivatives of this acid are described in the literature, it was synthesised from methyl hexyl ketone by

$$HC{:}C\cdot CH(OH)\cdot CH{:}CH_2 \quad (VI.)$$

means of a Reformatsky reaction and dehydration of the resultant hydroxy-ester followed by hydrogenation and hydrolysis. The p-*toluidides* prepared from the two specimens were identical. The facile rearrangement of the carbinol (I; $R_1 = R_2 = H$) is in striking contrast to the immobility of the hydroxyl group in the similarly constituted vinylethynylcarbinol (VI) (Jones and McCombie, J., 1943, 261) and phenylvinylcarbinol (Burton and Ingold, J., 1928, 904), indicating the surprisingly powerful influence of the tertiary methyl group.

Treatment of the carbinol (I; $R_1 = H$; $R_2 = Me$) from ethylideneacetone with either 0·5 or 5% sulphuric acid for 3 hours gave 4-*methyldec*-3-*en*-5-*yn*-2-*ol* (II; $R_1 = H$; $R_2 = Me$), characterised by the preparation of the *α-naphthylurethane*, in practically theoretical yield. Hydrogenation gave 4-*methyldecan*-2-*ol* (*α-naphthylurethane*), oxidised to 4-methyldecan-2-one, the semicarbazone of which had a somewhat higher m. p. than that given in the literature. Further structural proof was afforded by the hypobromite oxidation of the latter ketone to 2-*n*-hexylbutyric acid.

The conditions for the successful isomerisation of the carbinol (I; $R_1 = R_2 = Me$) from mesityl oxide were highly critical. With 0·5% sulphuric acid for 3 hours, conversion was incomplete, but after a further 2 hours an excellent yield of 2 : 4-*dimethyldec*-3-*en*-5-*yn*-2-*ol* (II; $R_1 = R_2 = Me$) was obtained. No crystalline derivatives could be prepared from this tertiary carbinol. Treatment of the original carbinol with 1% sulphuric acid for 24 hours gave a product (maximum at 2620 A.; $E^{1\%}_{1\,cm.}$ 410) which had undergone rearrangement followed by dehydration, and with 5% acid for the same time the product had a more complex absorption spectrum (maxima at 2640 and 2400 A.; $E^{1\%}_{1\,cm.}$ 360 and 320, respectively) indicating some dehydration of the rearranged carbinol and also some dehydration of the starting material

Further evidence of the lability of the anionotropic system present in carbinol (I; $R_1 = R_2 = Me$) was

obtained when mesityl oxide was condensed with hex-3-en-5-yn-2-ol (VII; cf. previous paper) by the Grignard method. The glycol (VIII), 2 : 4-*dimethyldeca*-2 : 7-*dien*-5-*yn*-4 : 9-*diol*, produced in 25% yield, underwent

$HC{:}C{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_3$ (VII.)
$CMe_2{:}CH{\cdot}C(OH)Me{\cdot}C{:}C{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_3$ (VIII.)

some rearrangement (as indicated by the appearance of an inflexion at 2630 A. in its absorption spectrum) even on distillation at 10^{-4} mm.

The absorption spectra (table) of the three pure isomerised carbinols (II), containing the conjugated vinylacetylene chromophore, are all closely analogous both amongst themselves and when compared with similar carbinols previously examined (*see* Parts VII, IX, X, XIV, and XV).

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{infl.}$, A.	$\varepsilon_{infl.}$
3-Methylnon-2-en-4-yn-1-ol (II; $R_1 = R_2 = H$)	2275	14,000	2350	11,000
4-Methyldec-3-en-5-yn-2-ol (II; $R_1 = H$; $R_2 = Me$)	2275	14,500	2320	8,000
2 : 4-Dimethyldec-3-en-5-yn-2-ol (II; $R_1 = R_2 = Me$) ...	2280	12,500	2400	7,500

In view of the unsatisfactory results attendant upon attempts to condense acetylene itself with αβ-ethylenic ketones, it was considered of interest to investigate the behaviour of αβ-acetylenic ketones in this respect. Oct-3-yn-2-one (IX) is a fairly readily accessible ketone of this type, having been prepared by Kroeger and Nieuwland (*J. Amer. Chem. Soc.*, 1936, **58**, 1862) by condensation of hexynylmagnesium chloride with acetic anhydride. After this substance (for which we are indebted to Mr. J. T. McCombie) had been kept with sodium acetylide (from sodium) in liquid ammonia, it was recovered almost quantitatively. With hexynylmagnesium bromide, however, it gave a 48% yield of 7-methyltrideca-5 : 8-diyn-7-ol (X), which had previously been

$CH_3{\cdot}[CH_2]_3{\cdot}C{:}C{\cdot}CO{\cdot}CH_3$ (IX.)
$CH_3{\cdot}[CH_2]_3{\cdot}C{:}C{\cdot}C(OH)Me{\cdot}C{:}C{\cdot}[CH_2]_3{\cdot}CH_3$ (X.)

obtained by Kroeger and Nieuwland (*loc. cit.*) as a by-product in the preparation of the ketone (IX). It is evident, therefore, that in condensations with substances containing free ethynyl groups, αβ-acetylenic ketones closely resemble the αβ-ethylenic compounds in that reaction with substituted acetylenes is more facile than with acetylene itself.

Experimental.

(Absorption spectra were determined in alcoholic solutions.)

3-*Methylnon*-1-*en*-4-*yn*-3-*ol* (I; $R_1 = R_2 = H$).—A solution of 1-hexyne (24 g.) in ether (400 c.c.) was added gradually to an ethereal solution of ethylmagnesium bromide (from 6 g. of magnesium), and the mixture refluxed for 3 hours. A solution of methyl vinyl ketone (17·5 g.) in ether (300 c.c.) was now dropped into the cooled reaction mixture in a nitrogen atmosphere, after which it was stirred vigorously for a further 3 hours and then set aside overnight. Subsequent isolation of the product in the usual manner yielded 3-*methylnon*-1-*en*-4-*yn*-3-*ol* (19·5 g.) as a colourless mobile liquid, b. p. 61—61·5°/3·5 mm., $n_D^{17°}$ 1·4593 (Found: C, 78·6; H, 10·5. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%). *Active hydrogen* (Zerewitinoff): The carbinol (90 mg.) evolved 15·0 c.c. of methane at 22°/756 mm., equivalent to 1·05 active hydrogen atoms per mol.

4-*Methyldec*-2-*en*-5-*yn*-4-*ol* (I; $R_1 = H$; $R_2 = Me$).—Condensation of hexynylmagnesium bromide, from 1-hexyne (22·5 g.) and magnesium (6 g.), with ethylideneacetone (20 g.) in ether (400 c.c.) gave the *carbinol* (20·7 g.) as a colourless mobile liquid, b. p. 62—62·5°/2 mm., $n_D^{19°}$ 1·4641 (Found: C, 79·75; H, 11·1. $C_{11}H_{18}O$ requires C, 79·45; H, 10·9%). *Active hydrogen* (Zerewitinoff): The carbinol (93 mg.) evolved 13·9 c.c. of methane at 25°/760 mm. (1·0 active hydrogen atom per mol.). Neither this nor the preceding compound showed appreciable light absorption in the ultra-violet.

2 : 4-*Dimethyldec*-2-*en*-5-*yn*-4-*ol* (I; $R_1 = R_2 = Me$).—By the method described above, 1-hexyne (11·3 g.), magnesium (3 g.), and mesityl oxide (12 g.) in ether (950 c.c.) afforded the *carbinol* (14·2 g.) as a colourless mobile liquid, b. p. 69—69·5°/3 mm., $n_D^{19°}$ 1·4673 (Found: C, 79·9; H, 11·3. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%). *Active hydrogen* (Zerewitinoff): The carbinol (102 mg.) gave 13·5 c.c. of methane at 21°/765 mm. (1·0 active hydrogen atom per mol.). It showed no absorption of appreciable intensity in the ultra-violet.

4-*Methyldec*-3-*en*-5-*yn*-2-*ol* (II; $R_1 = H$; $R_2 = Me$).—A mixture of 4-methyldec-2-en-5-yn-4-ol (12 g.) and sulphuric acid (2000 c.c.; 0·5% w/v) was shaken vigorously for 3 hours at 20°. Isolation of the product by means of ether yielded the *carbinol* (10·5 g.) as a colourless mobile liquid, b. p. 84°/2 mm., 28° (bath temp.)/10^{-4} mm., $n_D^{19°}$ 1·4786 (Found: C, 79·65; H, 11·0. $C_{11}H_{18}O$ requires C, 79·45; H, 10·9%). *Active hydrogen* (Zerewitinoff): The carbinol (94 mg.) gave 13·5 c.c. of methane at 23°/769 mm. (1·0 active hydrogen atom per mol.). The *α-naphthylurethane* separated from light petroleum (b. p. 40—60°) in needles, m. p. 71° (Found: N, 4·2. $C_{22}H_{25}O_2N$ requires N, 4·2%).

4-*Methyldecan*-2-*ol*.—A solution of 4-methyldec-3-en-5-yn-2-ol (5·4 g.) in ethyl acetate (100 c.c.) was shaken with platinic oxide (100 mg.) and hydrogen until absorption ceased. The catalyst was filtered off and the solvent removed through a column, leaving a residue of 4-*methyldecan*-2-*ol* (3·8 g.), b. p. 104°/12 mm., $n_D^{19°}$ 1·4332 (Found: C, 76·45; H, 13·8. $C_{11}H_{24}O$ requires C, 76·65; H, 14·05%). *Active hydrogen* (Zerewitinoff): The carbinol (105 mg.) gave 15·6 c.c. of methane at 28°/755 mm. (1·05 active hydrogen atoms per mol.). The *α-naphthylurethane* separated from methyl alcohol as needles, m. p. 63° (Found: N, 4·2. $C_{22}H_{31}O_2N$ requires N, 4·1%).

4-*Methyldecan*-2-*one*.—Oxidation of the above carbinol with chromic–sulphuric acid mixture gave the ketone, b. p. 95—96°/12 mm., $n_D^{21°}$ 1·4294. The semicarbazone separated from light petroleum (b. p. 40—60°) in plates, m. p. 69° (Found: C, 63·55; H, 11·0. Calc. for $C_{12}H_{25}ON_3$: C, 63·4; H, 11·1%). (Bouveault and Locquin, *Bull. Soc. chim.*, 1904, **31**, 1158, give b. p. 115°/25 mm. for the ketone and m. p. 66° for the semicarbazone.)

3-*Methylnon*-2-*en*-4-*yn*-1-*ol* (II; $R_1 = R_2 = H$).—A mixture of 3-methylnon-1-en-4-yn-3-ol (5·5 g.) and sulphuric acid (1000 c.c.; 0·5% w/v) was shaken at 20° under nitrogen for 4 hours. Isolation with ether gave 3-*methylnon*-2-*en*-4-*yn*-1-*ol* (4·9 g.) as a colourless mobile liquid, b. p. 75·5—76°/3·5 mm.; $n_D^{17°}$ 1·4858 (Found: C, 79·1; H, 10·45. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%). *Active hydrogen* (Zerewitinoff): The carbinol (90 mg.) evolved 15·1 c.c. of methane at 20°/766 mm. (1·05 active hydrogen atoms per mol.). The *α-naphthylurethane*, obtained after allowing the carbinol to react with α-naphthyl *iso*cyanate for only 6 hours at 20°, separated from methyl alcohol in needles, m. p. 69—70° (Found: N, 4·45. $C_{21}H_{23}O_2N$ requires N, 4·35%).

3-*Methylnonan*-1-*ol*.—A solution of the preceding carbinol (5·1 g.) in ethyl acetate (30 c.c.) together with platinic oxide

(100 mg.) was shaken with hydrogen until absorption was complete. Removal of the catalyst by filtration, followed by distillation of the solvent through a column, left a residue of 3-methylnonan-1-ol (5·0 g.), b. p. 121—121·5°/24 mm., $n_D^{16°}$ 1·4372 (Levene and Taylor, *J. Biol. Chem.*, 1922, **54**, 351, and Levene and Marker, *ibid.*, 1931, **91**, 77, give b. p. 122°/24 mm., $n_D^{25°}$ 1·4348). The *α-naphthylurethane* separated from alcohol in needles, m. p. 49° (Found : N, 4·45. $C_{21}H_{29}O_2N$ requires N, 4·3%).

2-n-*Hexylbutyric Acid.*—(a) A portion of a solution of methyl hexyl ketone (17 g.) and ethyl bromoacetate (22·5 g.) in dry benzene (300 c.c.) was added to zinc needles (9 g.), and the mixture heated under reflux with stirring. When reaction commenced, the remainder of the solution was dropped in during 2 hours, and refluxing and stirring were continued for 2 hours longer. The hydroxy-ester was isolated in the normal manner, and on heating it to 100—150°/760 mm., smooth dehydration occurred after which the unsaturated ester distilled at 237—238°. Redistillation gave ethyl 2-methyl-2-*n*-hexylacrylate (16·6 g.; 62% yield), b. p. 126—126·5°/18 mm., $n_D^{18°}$ 1·4460 (Bouveault and Blanc, *Bull. Soc. chim.*, 1904, **31**, 1208, give b. p. 119—120°/14 mm.).

A solution of the above ester (7·6 g.) in methyl alcohol (75 c.c.) was hydrogenated in the presence of platinic oxide (100 mg.), giving ethyl 2-*n*-hexylbutyrate (7·5 g.), b. p. 123·5°/24 mm., $n_D^{18°}$ 1·4268 (Levene *et al.*, *J. Biol. Chem.*, 1931, **91**, 77; 1922, **54**, 351, give b. p. 115°/13 mm., 135°/36 mm., $n_D^{25°}$ 1·4232). The ester was hydrolysed by refluxing with 25% alcoholic potassium hydroxide, yielding 2-*n*-hexylbutyric acid, b. p. 98—99°/2 mm., $n_D^{21°}$ 1·4352 (Chargaff and Abel, *Biochem. J.*, 1934, **28**, 1901, give b. p. 115—120°/3 mm.). The *p-toluidide*, prepared by heating the acid under reflux with *p*-toluidine, formed needles from alcohol, m. p. 76—77° (Found : C, 78·35; H, 10·45; N, 5·7. $C_{17}H_{27}ON$ requires C, 78·1; H, 10·4; N, 5·35%).

(b) Oxidation of 3-methylnonan-1-ol with chromic acid also gave 2-*n*-hexylbutyric acid, b. p. 162°/22 mm., $n_D^{17°}$ 1·4372 (Levene *et al.*, *loc. cit.*, give b. p. 147—148°/12 mm., 133°/8 mm., $n_D^{25°}$ 1·4339). The *p*-toluidide, prepared as above, had m. p. 76—77°, undepressed on admixture with the synthetic specimen.

(c) A mixture of 4-methyldecan-2-one (850 mg.) and sodium hypobromite solution (100 c.c.; 12%) was shaken at 20° for 43 hours. From the alkaline solution on acidification there were obtained 600 mg. of 2-*n*-hexylbutyric acid, b. p. 116—118°/3 mm., $n_D^{16°}$ 1·4384. The *p*-toluidide had m. p. 75—76°, undepressed on admixture with a synthetic specimen.

2 : 4-*Dimethyldec*-3-*en*-5-*yn*-2-*ol* (II; $R_1 = R_2 = Me$).—A mixture of 2 : 4-dimethyldec-2-en-5-yn-4-ol (2·4 g.) and sulphuric acid (500 c.c.; 0·5% w/v) was shaken vigorously for 5 hours at 20°, and isolation by means of ether yielded the *carbinol* (2·1 g.) as a colourless mobile liquid, b. p. 35° (bath temp.)/10^{-4} mm., $n_D^{18°}$ 1·4774 (Found : C, 79·9; H, 11·4. $C_{12}H_{20}O$ requires C, 79·9; H, 11·2%). *Active hydrogen* (Zerewitinoff) : The carbinol (103 mg.) gave 12·9 c.c. of methane at 21°/767 mm. (0·95 active hydrogen atom per mol.).

2 : 4-*Dimethyldeca*-2 : 7-*dien*-5-*yn*-4 : 9-*diol* (VIII).—Condensation between hex-3-en-5-yn-2-ol (6 g.) and mesityl oxide (6·1 g.) was effected in the usual manner, yielding the *glycol* (3·2 g.) as a pale yellow liquid, b. p. 60° (bath temp.)/10^{-4} mm., $n_D^{19°}$ 1·4962 (Found : C, 74·2; H, 9·6. $C_{13}H_{18}O_2$ requires C, 74·2; H, 9·35%). *Active hydrogen* (Zerewitinoff) : The glycol (91 mg.) evolved 22·9 c.c. of methane at 18°/758 mm. (2·0 active hydrogen atoms per mol.). *Light absorption :* Maximum, 2330 A.; $\varepsilon = 12{,}650$. Inflexion, 2630 A., $\varepsilon = 4400$.

7-*Methyltrideca*-5 : 8-*diyn*-7-*ol* (X).—Oct-3-yn-2-one (3·5 g.) was condensed with 1-hexyne (2·7 g.) by the Grignard method, 0·7 g. of magnesium being used. The reaction mixture was refluxed for 2½ hours, and the product then isolated in the usual manner. Distillation gave two fractions, (*a*) recovered ketone, b. p. 79—81°/20·5 mm. (1 g.) and (*b*) 7-methyltrideca-5 : 8-diyn-7-ol (1·9 g.), b. p. 149—149·5°/20·5 mm., which on redistillation had b. p. 100°/3 mm., $n_D^{21°}$ 1·4667 (Kroeger and Nieuwland, *loc. cit.*, give $n_D^{24°}$ 1·4660) (Found : C, 81·5. H, 10·55. Calc. for $C_{14}H_{22}O$: C, 81·5; H, 10·75%). *Active hydrogen* (Zerewitinoff) : The carbinol (102 mg.) evolved 12·8 c.c. of methane at 18°/772 mm. (1·15 active hydrogen atoms per mol.).

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Imperial College of Science and Technology, London, S.W.7. [*Received, November 3rd*, 1943.]

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53. *The Constitution of the So-called Carbothialdines and the Preparation of some Homologous Compounds.*

By A. D. Ainley, W. H. Davies, H. Gudgeon, J. C. Harland, and W. A. Sexton.

Consideration of methods of formation lead to structure (VI; R = H, R′ = Me) for "carbothialdine" (or "thiuram carbomethyl") and to (VI; R = Me, R′ = H) for the isomeric "dimethylformocarbothialdine" which is identical with "2 : 4-dimethyl-2-methylenecarbothialdine." Absorption spectra are in accord with the proposed formulæ. The preparation of homologous compounds by interaction of formaldehyde with primary aliphatic amine salts of monoaryldithiocarbamic acids is described.

Although the reaction products of aldehydes with carbon disulphide and ammonia or primary amines have been known for nearly a century, none of the formulæ suggested for them is entirely satisfactory. The best known of the series, the reaction product of acetaldehyde, ammonia, and carbon disulphide, is "carbothialdine," which, despite its name, has not been shown to be related to the thialdines which are 1 : 3 : 5-dithiazines formed by the action of hydrogen sulphide on aldehyde-ammonias.

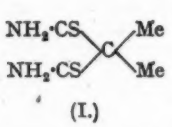
It appears to be generally agreed that the reaction of aldehydes (R″·CHO) with carbon disulphide and primary amines or ammonia (R′·NH_2) usually gives the same product as that obtained by reaction between the aldehyde and the dithiocarbamate NHR′·CS·SH,NH_2R′, and Levi (*Gazzetta*, 1931, **61**, 803) has shown that 2 mols. of aldehyde are involved in the reaction. He also showed (*ibid.*, 1930, **60**, 309) that potassium dithiocarbamates do not react with aldehydes.

"Carbothialdine" ($C_5H_{10}N_2S_2$) has been prepared by the action of carbon disulphide on acetaldehyde-ammonia (Redtenbacher and Liebig, *Annalen*, 1848, **65**, 43) and by condensing acetaldehyde with ammonium dithiocarbamate or trithiocarbonate (Mulder, *Annalen*, 1873, **168**, 228). The product is thermally unstable, decomposing at 120° according to Cohn (*Pharm. Zentr.*, 1910, **51**, 149), though in the present work material with higher decomposition point has been obtained. "Carbothialdine" is very difficult to purify owing to its

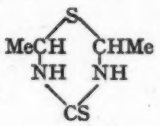
sensitivity even to solvents. It is reported to be soluble in dilute acids, though with decomposition (Mulder, *loc. cit.*). It is decomposed by water or alcohols, particularly when hot or in presence of acids; iodine, nitrous acid, or mercuric chloride causes a similar breakdown, ammonium thiocyanate being formed as well as the three main degradation products, acetaldehyde, ammonia, and carbon disulphide (Claus, *Ber.*, 1872, **5**, 362). Guareschi (*Gazzetta*, 1878, **8**, 246) reports that with ferric chloride, ferric thiocyanate is formed, but with ferric chloride in dilute acids or with chlorine water, the main product obtained is thiuram disulphide $(NH_2 \cdot CS \cdot S-)_2$, thus suggesting that the dithiocarbamate structure is present in the molecule. Oxidation with permanganate, however, converted all the sulphur into sulphuric acid; this showed that the presence of the group ·S·CHR·S· was unlikely, as known products of this type, such as thialdine and trithioacetaldehyde, on similar treatment give good yields of ethane-$\alpha\alpha$-disulphonic acid.

Mulder (*loc. cit.*) found that on treatment with certain heavy-metal salts, " carbothialdine " gave the corresponding metallic dithiocarbamate. Levi and Gimignani (*Gazzetta*, 1929, **59**, 757) showed that this reaction was more complex, and that unstable substituted dithiocarbamates containing aldehyde residues were also formed. These authors also studied alkylation of " carbothialdine " with methyl iodide and found the main product to be the hydriodide of dimethylthioformimine, $NH{:}C(SMe)_2$, a substance normally obtained by methylation of ammonium dithiocarbamate.

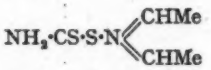
Four constitutional formulæ have been suggested for " carbothialdine." Hlasiwetz (*Ber.*, 1872, **5**, 803), without chemical evidence, put forward (I) by analogy with the thiuram sulphides, and suggested the name



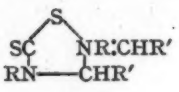
(I.)



(II.)



(III.)



(IV.)

" thiuram carbomethyl." Claus (*loc. cit.*) supported (II), originally proposed by Erlenmeyer, because he considered that the formation of thiocyanates in the decomposition reactions indicated that a thiourea group was present. This evidence is invalid, for it is known that aqueous ammonium dithiocarbamate, for example, readily gives ammonium thiocyanate on standing. Mulder (*loc. cit.*) proposed (III) to account for the ease with which metallic dithiocarbamates are formed on treating " carbothialdine " with heavy-metal salts. This formula was endorsed by Guareschi (*loc. cit.*) and has been accepted by Levi and Gimignani (*loc. cit.*) and by Powers (duPont, U.S.P., 1,732,532).

Delépine (*Bull. Soc. chim.*, 1897, **15**, 891) prepared an isomeric compound, " dimethylformocarbothialdine," m. p. 96°, by the action of carbon disulphide on trimethyltrimethylenetri-imine $(NMe{:}CH_2)_3$. As the Mulder type formula (III) could not be applicable to the new isomer, which from its formation must contain a methyl group attached to each nitrogen atom, Delépine suggested (IV; R = Me, R′ = H) for his new " dimethylformocarbothialdine," and (IV; R = H, R′ = Me) for " carbothialdine." He also showed that the new isomer on treatment with methyl iodide gave di(methylthio)-*N*-methylformimine (IX).

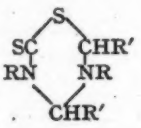
Bodendorf (*J. pr. Chem.*, 1930, **126**, 233) obtained from formaldehyde and methylammonium methyldithiocarbamate a compound, m. p. 106—107°, which he called " 2 : 4-dimethyl-2-methylenecarbothialdine " and to which he assigned the structure (IV; R = Me, R′ = H). Though no direct comparison appears to have been made, he assumed this to be the same as Delépine's " dimethylformocarbothialdine." We have now repeated both these preparations and find that the products are in fact identical.

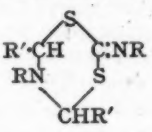
The four formulæ proposed are, however, all unsatisfactory. Neither (I) nor (II) accords with the methods of formation and properties as outlined above; (III) has already been rejected for a sufficient reason by Delépine (*loc. cit.*), and moreover, this formula would demand salt-like properties which are not characteristic of the " carbothialdines " : (IV) also contains quinquevalent nitrogen and so is quite incorrectly described as a 1 : 2 : 4-thiodiazole (cf. Bodendorf, *loc. cit.*). If this type of structure is to be postulated, the modern implication is the unusual betaine-like immonium type $\bar{S}{\cdot}CS{\cdot}NR{\cdot}CHR'{\cdot}\overset{+}{N}R{:}CHR'$ (V).

Alkyl-substituted immonium salts, $CR_2{:}\overset{+}{N}R_2\bar{X}$ have been described by Stewart and Bradley (*J. Amer. Chem. Soc.*, 1932, **54**, 4172) and Reiber and Stewart (*ibid.*, 1940, **62**, 3026). The conditions for the formation of such salts and their general properties are such that (V) does not give a satisfactory picture of the properties of the " carbothialdines." Furthermore, it is very doubtful whether such a formula would accord with the ultraviolet absorption data given below.

More rational formulæ may be derived by considering the probable mechanism of formation of " carbothialdine " from dithiocarbamic acid, ammonia, and acetaldehyde. McLeod and Robinson (J., 1921, **119**, 1470) have shown that thiols, formaldehyde, and amines react to give $SR{\cdot}CH_2{\cdot}NR_2$, a reaction which may proceed *via* the methylol derivative of either the amine (Robinson and Robinson, J., 1923, **123**, 532) or the thiol (Levi, *Gazzetta*, 1932, **62**, 775) : in either case, the intermediate methylol compound loses water by condensation with the third reactant. If a similar mechanism is applied to the case in which the thiol compound is dithiocarbamic acid and the aldehyde Me·CHO, an intermediate di(hydroxyethyl) compound of the type $CHMe(OH){\cdot}NH{\cdot}CS{\cdot}S{\cdot}CHMe{\cdot}OH$ or $NH{:}C(S{\cdot}CHMe{\cdot}OH)_2$ would be formed, which on condensation with ammonia would immediately cyclise to (VI or VII; R = H, R′ = Me). Either of these formulæ is in accord with the

known properties of " carbothialdine," and corresponding isomeric structures (VI or VII; R = Me, R′ = H) would then be probable for Delépine's " dimethylformocarbothialdine." We hoped to distinguish between

(VI.) 

(VII.) 

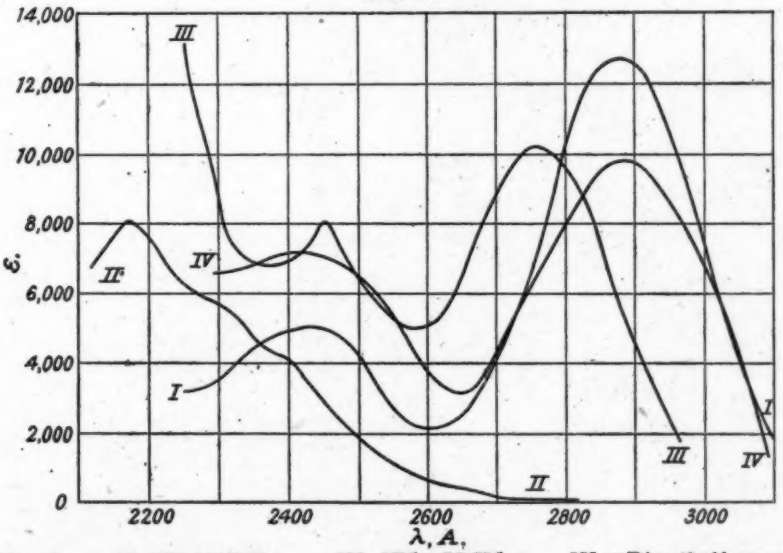
$NMe_2{\cdot}CS{\cdot}SMe$ (VIII.)

$NMe{:}C(SMe)_2$ (IX.)

the two types of structure by converting the thionlactone sulphur postulated by (VI) into oxygen by means of mercuric oxide, but under the mildest conditions " dimethylformocarbothialdine " (a more stable compound than " carbothialdine " itself) was completely disrupted.

The failure of chemical methods to decide the structure led us to examine the ultra-violet absorption spectra of the compounds. For this purpose " carbothialdine," " dimethylformocarbothialdine," methyl dimethyldithiocarbamate (VIII), analogous to (VI), and bismethylthio-*N*-methylformimine (IX), analogous to (VII), were examined. " Carbothialdine," " dimethylformocarbothialdine," and (VIII) gave similar types of curves with a marked peak between 2760 and 2890 A. and a subsidiary peak at about 2450 A.; (IX), on the other hand, gave only low general end absorption in this range (Fig. 1). It is concluded therefore that the available evidence

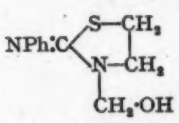
FIG. 1.



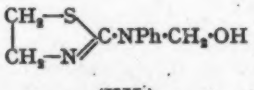
I. " Carbothialdine." II. $NMe{:}C(SMe)_2$. III. $NMe_2{\cdot}CS{\cdot}SMe$. IV. " Dimethylformocarbothialdine."

supports the structure (VI; R = H, R′ = Me) for " carbothialdine " or " thiuram carbomethyl " and (VI; R = Me, R′ = H) for " dimethylformocarbothialdine " or " 2 : 4-dimethyl-2-methylenecarbothialdine." On account of the derivation from the unknown 1 : 3 : 5-thiadiazine (X), these compounds should be named

(X.)



(XI.)



(XII.)

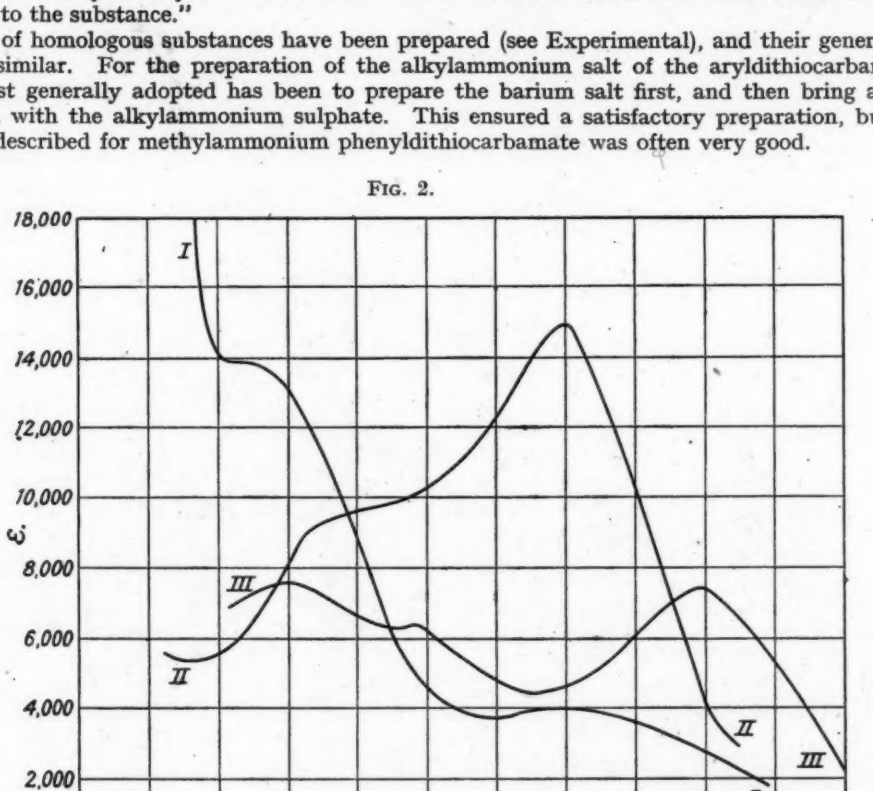
2-thio-4 : 6-dimethyltetrahydro-1 : 3 : 5-thiadiazine and 2-thio-3 : 5-dimethyltetrahydro-1 : 3 : 5-thiadiazine, respectively.

In the course of a study of the insecticidal and fungicidal properties of organic sulphur compounds (British Patent Specifications Nos. 554,729 and 555,795), we have prepared a series of 2-thio-3-aryl-5-alkyltetrahydro-1 : 3 : 5-thiadiazines. Methylammonium phenyldithiocarbamate (made by direct interaction of aniline, carbon disulphide, and aqueous methylamine) reacts rapidly with aqueous formaldehyde, precipitating *2-thio-3-phenyl-5-methyltetrahydro*-1 : 3 : 5-*thiadiazine* (type VI) in good yield. This is a crystalline compound, stable on storage in a dry state, very slowly decomposed by cold water and more rapidly by boiling water. Like the 3 : 5-dimethyl compound, it is completely decomposed under mild conditions by dilute acids or by mercuric oxide, and it is not possible to establish its structure by chemical degradation. Any doubt between the two possible formulæ of type (VI) and (VII) has been removed by a comparison of the ultra-violet spectrum of the compound with those of the " model " compounds, $NPhMe{\cdot}CS{\cdot}SMe$ and $NPh{:}C(SMe)_2$.

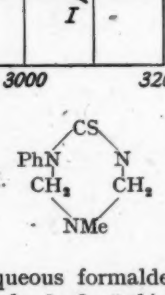
For the following comments on the results, we are indebted to Dr. R. A. Morton of Liverpool University. "The compound $NMe{:}C(SMe)_2$ (Fig. 1) has no powerful chromophore. The phenyl analogue $NPh{:}C(SMe)_2$ shows a spectrum (Fig. 2) probably due to the NPh: group, modified a little by the rest of the molecule, which however makes no direct contribution to the absorption. In $NMe_2{\cdot}CS{\cdot}SMe$ (Fig. 1), it seems certain that ·CS·S· includes the absorbing unit, and in NPhMe·CS·SMe the contribution by NPh· is superimposed. Sufficient information is not available to assess the mutual effects of the NPh· and the ·CS·S· chromophore, but the additive nature of the curve is not to be doubted. In consequence, the two bands at *ca.* 2900 and 2430 A. in 2-thio-3-phenyl-5-methyltetrahydro-1 : 3 : 5-thiadiazine are consistent with the formula and name which have been assigned to the substance."

A number of homologous substances have been prepared (see Experimental), and their general properties have proved similar. For the preparation of the alkylammonium salt of the aryldithiocarbamic acid the procedure most generally adopted has been to prepare the barium salt first, and then bring about double decomposition with the alkylammonium sulphate. This ensured a satisfactory preparation, but the direct formation as described for methylammonium phenyldithiocarbamate was often very good.

FIG. 2.



I. $NPh{:}C(SMe)_2$. II. NMePh·CS·SMe. III.



Treatment of β-hydroxyethylammonium phenyldithiocarbamate with aqueous formaldehyde affords a mixture containing 75% of the expected *2-thio-3-phenyl-5-(β-hydroxyethyl)tetrahydro*-1 : 3 : 5-*thiadiazine* together with 25% of a substance believed to be a *hydroxymethyl* derivative of 2-anilino-4 : 5-dihydrothiazole (XI or XII), since acid hydrolysis liberated formaldehyde and the (tautomeric) base. The latter was identified, together with its picrate, by mixed m. p. with authentic material. The available evidence is insufficient to adjudicate between formulæ (XI) and (XII). However, it is clear that formaldehyde plays an essential part in the cyclisation, since (i) in its absence, aqueous β-hydroxyethylammonium phenyldithiocarbamate remained substantially unchanged for several days at room temperature, and (ii) 2-anilinodihydrothiazole failed to react with formaldehyde at room temperature. It follows from (ii) that attachment of $\cdot CH_2{\cdot}OH$ to nitrogen precedes cyclisation.

Reaction of alcoholic *p*-anisidine, *p*-aminodimethylaniline, and *p*-aminodiethylaniline with carbon disulphide gave the aromatic base salts of the substituted phenyldithiocarbamic acids. Such salts are uncommon and are only known for a few of the stronger aromatic bases such as *p*-phenetidine (Hugershoff, *Ber.*, 1899, **32**, 2245). p-*Diethylaminophenylammonium* p-*diethylaminophenyldithiocarbamate* was indeed formed so readily that it seriously interfered with the formation of ammonium and sodium salts of the dithiocarbamic acid by

reaction of ammonia and sodium carbonate respectively with carbon disulphide and the aromatic base. This is in accordance with the fact that diethylaniline is a much stronger base than dimethylaniline (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469).

Experimental.

A. *Preparation of Compounds.*—2-*Thio*-4 : 6-*dimethyltetrahydro*-1 : 3 : 5-*thiadiazine* ("*Carbothialdine*") (VI; R = H, R′ = Me). This was obtained by the method of Redtenbacher and Liebig (*loc. cit.*), and purified after considerable difficulty by crystallisation first from methyl alcohol and finally from ethyl alcohol–ethyl acetate; m. p. 135° (decomp.) (Found: C, 37·4; H, 6·3; N, 16·8; S, 40·0. Calc. for $C_5H_{10}N_2S_2$: C, 37·0; H, 6·2; N, 17·5; S, 39·5%).

2-*Thio*-3 : 5-*dimethyltetrahydro*-1 : 3 : 5-*thiadiazine* ("*dimethylformocarbothialdine*") (VI; R = Me, R′ = H). Specimens of this substance were made (a) by Delépine's method (*loc. cit.*) from trimethyltrimethylenetri-imine and carbon disulphide and (b) by Bodendorf's method (*loc. cit.*) from methylammonium methyldithiocarbamate and formaldehyde. Both specimens had m. p. 106° (from benzene) and gave no depression on mixing. Delépine gives m. p. 96°, and Bodendorf 106—107°.

Methyl dimethyldithiocarbamate (VIII). A mixture of 25·3% aqueous dimethylamine (88 c.c.), 31% aqueous sodium hydroxide (48 c.c.), and water (50 c.c.) was treated with stirring with carbon disulphide (30·5 c.c.) at 25° for 1 hour. Methyl sulphate (47·3 c.c.) was then run in, the temperature being kept at 30—40°. After 1 hour's stirring the ester was extracted with ether, washed, dried (magnesium sulphate), and distilled, giving a yellowish solid (52 g.), b. p. 125—126°/17 mm. Recrystallisation from methyl alcohol and from light petroleum (b. p. 40—60°) gave white prisms, m. p. 45—46°.

Bismethylthio-N-*methylformimine* (IX). Methyl methyldithiocarbamate (30·3 g.; prepared from methylamine by the method used for the dimethyl derivative) in methyl alcohol (30 c.c.) was treated at 25—30° with methyl iodide (15·5 c.c.). After several hours' stirring, water was added to dissolve the precipitated hydriodide of the formimine. The solution was treated with charcoal, filtered, and made just alkaline to brilliant-yellow with sodium hydroxide. The yellow oil was extracted with ether and distilled, giving bismethylthio-*N*-methylformimine (26·2 g.), b. p. 188—192°.

2-*Thio*-3-*phenyl*-5-*methyltetrahydro*-1 : 3 : 5-*thiadiazine*. A stirred mixture of aniline (22·7 c.c.), carbon disulphide (15 c.c.), and water (100 c.c.) was treated during 20 minutes at room temperature with 10% aqueous methylamine solution (78 c.c.). After 2 hours' stirring, the solution was diluted to 2 l., filtered from a little insoluble material, and treated during 10 minutes, while stirred at 10°, with a solution of 37% formaldehyde (38 c.c.) in water (100 c.c.). After stirring for 1 hour, the precipitated solid was separated and dried (40 g.; 70%), and after crystallising from benzene had m. p. 148° (Found: C, 54·0; H, 5·5; N, 12·2; S, 28·6. $C_{10}H_{12}N_2S_2$ requires C, 53·6; H, 5·4; N, 12·5; S, 28·6%).

The same *compound* was prepared in somewhat better yield (80%) by interaction between equimolecular quantities of sodium carbonate, aniline, and carbon disulphide in water at 20—30° to yield sodium phenyldithiocarbamate solution, which, after addition of 2 mols. of formaldehyde in diluted solution and filtration from a slight sticky deposit, was treated at room temperature with 1 mol. of neutral aqueous methylammonium sulphate.

Substituted 2-*Thio*-3-*aryl*-5-*alkyltetrahydro*-1 : 3 : 5-*thiadiazines*.—The substances described below were obtained by one of two general methods. (1) The barium salt of the aryldithiocarbamic acid was precipitated by addition of barium chloride to a solution of the ammonium salt, and this was followed by double decomposition with the sulphate of the aliphatic amine. After separation of barium sulphate, formaldehyde was added, and the precipitated reaction product separated, dried, and crystallised from an appropriate solvent. (2) This was used in the case of the aminophenols. It is similar to method (1) except that the starting point was the sodium salt of the aryldithiocarbamic acid (instead of the ammonium salt), prepared from the sodium salt of the appropriate aminophenol.

2-*Thio*-3-α-*naphthyl*-5-*methyltetrahydro*-1 : 3 : 5-*thiadiazine* (Method 1), m. p. 159—160° (from benzene) (Found: C, 61·8; H, 5·0; N, 10·0; S, 23·0. $C_{14}H_{14}N_2S_2$ requires C, 61·3; H, 5·4; N, 10·2; S, 23·4%); 3-p-*chlorophenyl* analogue (Method 1), m. p. 139—140° (from dichloroethane) (Found: N, 10·5; Cl, 13·8. $C_{10}H_{11}N_2S_2Cl$ requires N, 10·8; Cl, 13·7%); 3-p-*anisyl* compound (Method 1), m. p. 160—161° (from dichloroethane) (Found: N, 11·1; S, 25·6. $C_{11}H_{14}ON_2S_2$ requires N, 11·0; S, 25·2%). An attempt to prepare the last substance by direct interaction of *p*-anisidine, methylamine, carbon disulphide, and formaldehyde failed owing to the formation of the *p*-anisidine salt of the aryldithiocarbamic acid.

2-*Thio*-3-(p-*hydroxyphenyl*)-5-*methyltetrahydro*-1 : 3 : 5-*thiadiazine* (Method 2), m. p. 163—164° (from ethyl alcohol) (Found: N, 11·5; S, 26·6. $C_{10}H_{12}ON_2S_2$ requires N, 11·7; S, 26·7%); 3-(3′-*chloro*-4′-*hydroxy*)-compound (Method 2), m. p. 146° (from alcohol or benzene–alcohol) (Found: N, 10·0; Cl, 12·5. $C_{10}H_{11}ON_2S_2Cl$ requires N, 10·2; Cl, 12·7%); 3-(p-*dimethylaminophenyl*) compound (Method 1), m. p. 168—169° (from acetone) (Found: N, 15·5; S, 24·4. $C_{12}H_{17}N_3S_2$ requires N, 15·7; S, 24·0%): addition of carbon disulphide (1·3 c.c.) to *p*-aminodimethylaniline (2·7 g.) in alcohol (10 c.c.) gave pale yellow crystals (m. p. 94—96°, decomp.) of the amine dithiocarbamate. Similarly, with *p*-aminodiethylaniline, p-*diethylaminophenylammonium* p-*diethylaminophenyldithiocarbamate* was obtained as yellow crystals, m. p. 97—99° (Found: N, 13·8. $C_{20}H_{32}N_4S_2$ requires N, 13·9%). This reaction interfered with the preparation of the thiadiazine by both methods (1) and (2).

2-*Thio*-3-*phenyl*-5-(β-*diethylaminoethyl*)*tetrahydro*-1 : 3 : 5-*thiadiazine* (Method 1), m. p. 103—104° (from benzene–light petroleum) (Found: C, 58·8; H, 7·6; N, 13·6. $C_{15}H_{23}N_3S_2$ requires C, 58·5; H, 7·5; N, 13·6%). The 5-(β-*hydroxyethyl*) analogue of this was obtained by Method 1 in a yield of 13 g. after recrystallisation from acetone (300 c.c.); m. p. 136° (not raised further by another crystallisation) (Found: N, 11·1; S, 25·3. $C_{11}H_{14}ON_2S_2$ requires N, 11·0; S, 25·2%); the crude product weighed 30 g.

Hydroxymethyl derivative of 2-*anilino*-4 : 5-*dihydrothiazole*. The mother-liquors from the above acetone crystallisation were concentrated, giving three successive crops of crystals, which were combined and recrystallised to constant m. p. from ethyl acetate; yield 6·0 g., m. p. 165° (Found: C, 57·2; H, 5·7; N, 13·5; S, 15·6. $C_{10}H_{12}ON_2S$ requires C, 57·6; H, 5·8; N, 13·6; S, 15·4%). On boiling with dilute sulphuric acid, the *compound* evolved formaldehyde, and when the cooled liquid was made alkaline, anilinodihydrothiazole was precipitated, m. p. (from benzene) 160—161°; picrate, m. p. 201—205° (from alcohol). Neither the base nor its picrate gave m. p. depressions when mixed with authentic samples. The base was prepared by the action of concentrated hydrochloric acid on *N*-phenyl-*N*′-β-hydroxyethylthiourea (cf. Dains *et al.*, *J. Amer. Chem. Soc.*, 1925, **47**, 1981) and had m. p. 160°, picrate m. p. 201—203° (Menne, *Ber.*, 1900, **33**, 657, gives 159—160° and 198—202°, respectively). 2-Anilinodihydrothiazole failed to react with formaldehyde when heated for 20 hours at 70—80° in aqueous-alcoholic solution. β-Hydroxyethylammonium phenyldithiocarbamate very slowly deposited thiocarbanilide, but otherwise remained unchanged in aqueous solution during 3 days at room temperature.

B. *Absorption Spectra* (with F. R. Cropper).—The compounds were dissolved in cold *cyclo*hexane (with the exception of "carbothialdine" which, being very sparingly soluble in *cyclo*hexane, was examined in ethyl alcohol) in concentrations from 0·45 mg. to 10·4 mg. per 50 ml., in 1 mm., 5 mm., and 2 cm. cells. The solvents had been purified by standard methods (*cyclo*hexane, extracted with oleum, washed, dried and distilled; ethyl alcohol, distilled from solid potassium hydroxide and silver nitrate).

The absorption-spectra determinations were carried out on a Hilger E498 Medium Quartz Spectrograph, with a "Spekker" photometer. The results are summarised in the following table, and plotted in Figs. 1 and 2.

Substance.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{min.}$, A.	$\varepsilon_{min.}$
"Carbothialdine"	2880	12,800	2620	2100
	2430	5,000	—	—
"Dimethylformocarbothialdine"	2890	9,900	2640	3100
	2420	7,150	—	—
Methyl dimethyldithiocarbamate	2760	10,100	2600	4950
	2460	8,000	2370	6750
Bismethylthio-*N*-methylformimine	2170	*ca.* 8,000	—	—
2-Thio-3-phenyl-5-methyltetrahydro-1 : 3 : 5-thiadiazine	2990	7,500	—	—
	2580	6,400	2760	4400
	2410	7,600	2560	6150
Methyl phenylmethyldithiocarbamate	2800	15,000	2260	*ca.* 5300
	2400—2650 *	10,000	—	—
Bismethylthio-*N*-phenylformimine	280	4,100	2690	3700
	2330—2370 *	*ca.* 14,100	—	—

* Inflexion.

The last three compounds in the table were examined in alcohol as well as in *cyclo*hexane, and no significant differences were observed.

The authors thank Imperial Chemicals Industries Limited for permission to publish these results.

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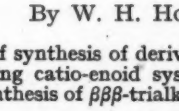
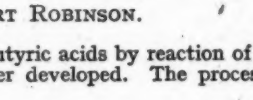
54. *Long-chain Acids containing a Quaternary Carbon Atom. Part III.*

By W. H. HOOK and SIR ROBERT ROBINSON.

The general method of synthesis of derivatives of ββ-dialkylbutyric acids by reaction of Grignard reagents with substances containing catio-enoid systems has been further developed. The process has been shown to be applicable to the synthesis of βββ-trialkylpropionic acids.

THE work of Adams and his collaborators (*J. Amer. Chem. Soc.*, 1929, **51**, 1261; and earlier papers) has shown that dialkylacetic acids containing from 16 to 18 carbon atoms possess some bactericidal properties against *Mycobacterium tuberculosis*. More recently Birch and Robinson (J., 1942, 488), citing a report by Stenhagen, have indicated that certain ββ-dialkylbutyric acids which they prepared are equally effective, and have the advantage that they are less irritant to living tissue. As the method used for the synthesis of ββ-di-*n*-octylbutyric acid, for example, was very laborious and gave rather low yields, the present work was undertaken in order to find a better method of synthesis of ββ-dialkylbutyric acids, so that their biological properties might be more fully investigated.

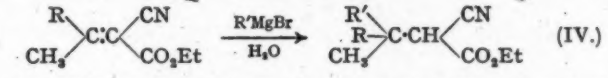
Kharasch (*J. Amer. Chem. Soc.*, 1941, **63**, 2308) has shown that the reaction of a Grignard reagent with an αβ-unsaturated ketone is substantially affected by the presence of certain metallic salts as catalysts. For instance, although the normal reaction between isophorone and methylmagnesium bromide proceeds at the carbonyl group, he has shown that in the presence of cuprous chloride the 1 : 4-addition predominates, the main product being a saturated ketone. This observation suggested that the action of a Grignard reagent on a ketone of the type (I), followed by oxidation, might yield the ββ-dialkylbutyric acids (II), but study of the

(I.)   (II.)

reaction between 8-keto-6-methyltridec-6-ene (I, R = C_5H_{11}) and *n*-amylmagnesium bromide in the presence of cuprous bromide showed that addition occurred in the 1 : 2- and 1 : 4-positions in about equal proportions. The reaction also proved to be very sluggish, and the difficulty experienced in separating the products from unchanged starting material and from one another rendered this scheme of little practical value. During the course of this investigation it was found that the reaction between the αβ-unsaturated ketone and amylmagnesium bromide proceeded more rapidly in the presence of cuprous iodide than in that of cuprous bromide. It was also found that methylmagnesium iodide reacts with 8-keto-6-methyltridec-6-ene in the presence of a cuprous salt to give a much higher proportion of the 1 : 2-addition product than does *n*-amylmagnesium bromide. This is not surprising in view of the finding of Colonge (*Bull. Soc. chim.*, 1935, **2**, 754) that 2-keto-3-methylpent-3-ene reacted with methylmagnesium iodide in the absence of a catalyst to give only the unsaturated tertiary alcohol, but with ethylmagnesium bromide to give a mixture of tertiary alcohol and saturated ketone.

In view of the above results, it seemed of interest to test the action of Grignard reagents on suitable substances containing a more highly activated double bond as a means of building up the quaternary carbon atom in ββ-dialkylbutyric acids. Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 333) found that phenylmagnesium bromide reacted quantitatively with ethyl α-cyanocinnamate to give ethyl α-cyano-ββ-diphenylpropionate. This method was found to be of general application, and the alkylidenecyanoacetates (III)

were converted by alkylmagnesium bromides into α-cyano-ββ-dialkylbutyrates (IV) in 66% yield (cf. Birch and Robinson, J., 1943, 501). Some reduction of the alkylidenecyanoacetate to the saturated α-cyano-β-alkyl-



butyric ester also occurred in the presence of the Grignard reagent, but the amount of reduction product was reduced to a minimum by adding the Grignard reagent slowly to the alkylidenecyanoacetate. Cuprous iodide as catalyst facilitated the reaction.

Hydrolysis of the α-cyano-ββ-dialkylbutyric ester (IV) to the ββ-dialkylbutyric acid at first presented some difficulty. αα-Dicyano-β-methyl-β-hexylglutarimide was hydrolysed by Birch and Robinson (*loc. cit.*) to β-methyl-β-hexylglutaric acid by refluxing with a mixture of sulphuric acid, acetic acid, and water, but prolonged treatment of the ethyl α-cyano-ββ-dialkylbutyrates in a similar way gave very unsatisfactory results. Vogel (J., 1928, 2010) hydrolysed a number of α-cyano-esters to the malonic acids with alcoholic potassium hydroxide, but with the present examples, prolonged treatment with aqueous and alcoholic alkali, or with alkali in high-boiling solvents such as *cyclo*hexanol (cf. B.P. 469,921; *Chem. Abstr.*, 1938, 729) proved equally ineffective. Heating with alcohol and sulphuric acid under pressure resulted in almost complete recovery of the α-cyano-ester, and keeping for several days with cold concentrated sulphuric acid yielded no useful product. The presence of the cyano-acid in some of the hydrolysis products after distillation indicated that this acid was unexpectedly stable, and experiment showed that no decarboxylation occurred below 200° except in the presence of copper powder. It seemed likely, therefore, that no decarboxylation of the cyano-acid occurred under the conditions used in the attempted acid hydrolysis.

Eventually the α-cyano-ββ-dialkylbutyric esters were hydrolysed to the cyano-acids with aqueous sodium hydroxide, and decarboxylated by heating with copper powder. Treatment of the nitriles so obtained with a mixture of sulphuric acid, acetic acid, and water then gave the ββ-dialkylbutyric acids in good yield.

β-n-*Amyl*-β-n-*heptylbutyric acid*, β-n-*butyl*-β-n-*nonylbutyric acid*, ββ-*di*-n-*heptylbutyric acid*, and β-*propyl*-ββ-*di*iso*amylpropionic acid* have been prepared by this method; they are colourless, viscous oils, which form sparingly soluble alkali-metal salts. With the exception of β-*propyl*-ββ-*di*iso*amylpropionamide*, the amides were very viscous oils which showed no tendency to crystallise.

Some difficulty was experienced throughout this work in obtaining consistent analyses of these quaternary compounds; purity of the products was therefore checked at most stages by a determination of the molecular refraction.

Specimens of the above acids have been submitted for biological tests, and preliminary results indicate that the C_{16} acids are the most active bactericidally, but they are not more active than diheptylacetic acid.

Experimental.

8-*Keto*-6-*methyl*-6-n-*amyltridecane*.—Methyl *n*-amyl ketone was condensed in the presence of methylanilinomagnesium bromide (Colonge, *Bull. Soc. chim.*, 1934, **1**, 1101), and the product dehydrated over iodine at 170° and distilled. 8-Keto-6-methyltridec-6-ene was obtained as a pale yellow oil boiling at 148—150°/19 mm. The unsaturated ketone (20 g.) in ether (30 c.c.) was slowly stirred into a cooled Grignard solution from magnesium (4·8 g.) and *n*-amyl bromide (40 g.) in ether (80 c.c.), to which cuprous bromide (0·2 g.) had been added. The mixture was refluxed for 20 hours and kept for 4 days. It was then decomposed with water and dilute hydrochloric acid, heated with iodine to dehydrate any carbinol, and distilled. The higher-boiling product was refluxed for 6 hours with 60% sulphuric acid and steam-distilled. The oily separated layer gave 4·0 g., b. p. 160—175°/18 mm. (Found: C, 82·5; H, 13·3. $C_{19}H_{38}O$ requires C, 80·8; H, 13·5. $C_{19}H_{36}$ requires C, 86·4; H, 13·6%). This product was dissolved in acetone and treated with powdered potassium permanganate (1·7 g.) with stirring, the temperature being maintained below 20°. On working up, 8-*keto*-6-*methyl*-6-n-*amyltridecane* (2·0 g.), b. p. 165—170°/19 mm., was obtained (Found: C, 81·0; H, 13·3%); the 2 : 4-dinitrophenylhydrazone was a dark red oil.

ββ-*Di*-n-*amylbutyric Acid*.—Ethyl 1-methylhexylidenecyanoacetate (29 g.), obtained by the method of Cope (*J. Amer. Chem. Soc.*, 1941, **63**, 3454), in ether (60 c.c.) was slowly added with stirring at 10—15° during ½ hour to a Grignard reagent, prepared from magnesium (5·8 g.), *n*-amyl bromide (40 g.), and ether (110 c.c.), to which cuprous iodide (0·5 g.) had been added. The mixture was refluxed for an hour, and after keeping for a further 2 hours was decomposed with ice and acetic acid (20 c.c.). The ethereal layer was washed with water, aqueous sodium bicarbonate, and with water, and dried over sodium sulphate. Fractionation by means of a heated column yielded *ethyl* α-*cyano*-ββ-*di*-n-*amylbutyrate* as a colourless oil (14 g.), b. p. 137—139°/0·3 mm. (Found: C, 72·2; H, 10·8; N, 5·1. $C_{17}H_{31}O_2N$ requires C, 72·6; H, 11·0; N, 5·0%).

A lower-boiling fraction was shaken for 10 hours with a 20% solution of sodium bisulphite to remove unchanged alkylidenecyanoacetate, and the insoluble moiety collected with benzene and distilled through a column. *Ethyl* α-*cyano*-β-*methyloctoate* was obtained as a colourless mobile oil, b. p. 90—92°/0·1 mm. (Found: C, 68·1; H, 9·9; N, 6·5. $C_{12}H_{21}O_2N$ requires C, 68·3; H, 10·0; N, 6·6%).

Ethyl cyanodiamylbutyrate (5 g.) was refluxed for 12 hours with a mixture of sulphuric acid (10 c.c.), acetic acid (20 c.c.), and water (10 c.c.). The product was poured into water, extracted with ether, and washed thoroughly with water. After drying and removal of the solvent, it was heated to 160° in a vacuum to complete decarboxylation of any amido-acid. The product was then dissolved in light petroleum, and extraction with dilute aqueous sodium hydroxide yielded ββ-*di*-n-*amylbutyric acid* (0·3 g.), b. p. 125—130°/0·3 mm. (Found: C, 74·3; H, 12·2. $C_{14}H_{28}O_2$ requires C, 73·7; H, 12·3%).

β-n-*Butyl*-β-n-*nonylbutyric Acid*.—*Ethyl* 1-*methyldecylidenecyanoacetate* (26 g.) was obtained from methyl *n*-nonyl ketone (26 g.) and ethyl cyanoacetate (17 g.) by Cope's method (*loc. cit.*) as a pale yellow oil, b. p. 146—148°/0·25 mm. (Found: C, 72·6; H, 10·3; N, 5·4. $C_{18}H_{33}O_2N$ requires C, 72·5; H, 10·2; N, 5·3%).

The Grignard solution prepared from magnesium (4·0 g.), *n*-butyl bromide (27 g.), and ether (80 c.c.) was added slowly with stirring, during 20 minutes at 15—20°, to a solution of ethyl methyldecylidenecyanoacetate (30 g.) in ether (60 c.c.)

in which was suspended cuprous iodide (0·5 g.). The mixture was refluxed for an hour and kept for a further 2 hours. *Ethyl α-cyano-β-*n*-butyl-β-*n*-nonylbutyrate* was isolated in the usual way as an almost colourless oil, b. p. 150—160°/0·2 mm. (21 g.) (Found : C, 74·4; H, 11·4; N, 4·4. $C_{20}H_{37}O_2N$ requires C, 74·3; H, 11·4; N, 4·3%); $n_D^{20°}$ 1·4537; $d^{20°}$ 0·9108; $[R_L]_D$ 95·99 (calc., 95·96).

Ethyl cyano-*n*-butyl-*n*-nonylbutyrate was hydrolysed by boiling, with stirring, for 3 hours with 5 times its weight of 10% aqueous sodium hydroxide and a little alcohol. The acidic product was isolated and heated to 180° in a vacuum with a little copper powder until decarboxylation was complete. *β-*n*-Butyl-β-*n*-nonylbutyronitrile* was a colourless mobile oil, b. p. 130—136°/0·3 mm. (Found : C, 81·1; H, 13·3; N, 5·9. $C_{17}H_{33}N$ requires C, 81·3; H, 13·1; N, 5·6%); $n_D^{20°}$ 1·4489; $d^{20°}$ 0·8364; $[R_L]_D$ 80·48 (calc., 80·45).

An intermediate fraction from the preparation of ethyl cyano-*n*-butyl-*n*-nonylbutyrate was hydrolysed and decarboxylated as above, and after distillation, a small quantity of a white solid crystallised from the distillate. This proved to be *β-methyldodecamide*; it crystallised from light petroleum in white needles, m. p. 87° (Found : C, 73·1; H, 12·7; N, 6·7. $C_{13}H_{27}ON$ requires C, 73·2; H, 12·7; N, 6·6%).

A mixture of *n*-butyl-*n*-nonylbutyronitrile (10 g.), acetic acid (40 c.c.), sulphuric acid (20 c.c.), and water (16 c.c.) was refluxed for 12 hours. The upper layer disappeared after about an hour, and after 2—3 hours the solution became cloudy, and an upper layer again began to separate. After 12 hours water was added, and the product isolated by means of ether. It was refluxed for 4 hours with methanol (50 c.c.) and sulphuric acid (2·5 c.c.). The solution was concentrated to half its volume, and the ester then separated by addition of water and extraction with ether. *Methyl β-*n*-butyl-β-*n*-nonylbutyrate* was obtained as a colourless mobile oil (5·6 g.), b. p. 116—120°/0·1 mm. (Found : C, 76·1; H, 12·7. $C_{19}H_{38}O_2$ requires C, 76·1; H, 12·7%); $n_D^{20°}$ 1·4456; $d^{20°}$ 0·8708; $[R_L]_D$ 86·89 (calc., 86·98).

The higher-boiling residue from the above hydrolysis was distilled, and *β-*n*-butyl-β-*n*-nonylbutyramide* was obtained as a very viscous, colourless oil, b. p. 165—180°/0·45 mm., which could not be induced to crystallise (Found : C, 75·9; H, 12·8; N, 5·2. $C_{17}H_{35}ON$ requires C, 75·8; H, 13·0; N, 5·2%); $n_D^{20°}$ 1·4677; $d^{20°}$ 0·8899; $[R_L]_D$ 84·06 (calc., 84·14). Hydrolysis of the amide with sulphuric and acetic acids and esterification as above yielded a further quantity of the methyl ester.

A mixture of methyl *n*-butyl-*n*-nonylbutyrate (7 g.), potassium hydroxide (5 g.), alcohol (30 c.c.), and water (20 c.c.) was refluxed for 2 hours. The alcohol was then removed, and the acidic product isolated in the known manner; *β-*n*-butyl-β-*n*-nonylbutyric acid* was obtained as a viscous, colourless oil, b. p. 155—157°/0·3 mm. (Found : C, 75·3; H, 12·6. $C_{17}H_{34}O_2$ requires C, 75·6; H, 12·6%); $n_D^{20°}$ 1·4539; $d^{20°}$ 0·8889; $[R_L]_D$ 82·25 (calc., 82·24).

*β-*n*-Amyl-β-*n*-heptylbutyric Acid.*—The Grignard solution prepared from magnesium (5·4 g.), heptyl bromide (41 g.), and ether (120 c.c.) was caused to react with ethyl 1-methylhexylidenecyanoacetate (34 g.) in ether (60 c.c.) as described for ethyl cyano-*n*-butyl-*n*-nonylbutyrate. On working up the product, *ethyl α-cyano-β-*n*-amyl-β-*n*-heptylbutyrate* was obtained as an almost colourless oil (33 g.), b. p. 155—158°/·012 mm. (Found : C, 74·0; H, 11·3; N, 4·8. $C_{19}H_{35}O_2N$ requires C, 73·8; H, 11·3; N, 4·5%); $n_D^{20°}$ 1·4522; $d^{20°}$ 0·9125; $[R_L]_D$ 91·39 (calc., 91·34).

The lower-boiling fraction was shaken with concentrated sulphuric acid, washed with water, dried, and distilled. The product was found to be *n*-tetradecane, b. p. 122—123°/14 mm., m. p. 5·5° (Kraft, *Ber.*, 1886, **19**, 2218, gives m. p. 5·5°); $n^{20°}$ 1·4293 (Found : C, 85·0; H, 15·1. Calc. for $C_{14}H_{30}$: C, 84·9; H, 15·1%).

Ethyl α-cyano-*β-n*-amyl-*β-n*-heptylbutyrate was hydrolysed to the dialkylbutyric acid as described for ethyl cyano-*n*-butyl-*n*-nonylbutyrate. *β-*n*-Amyl-β-*n*-heptylbutyronitrile* was obtained as a colourless oil, b. p. 123—126°/0·25 mm. (Found : C, 80·7; H, 13·1; N, 6·1. $C_{16}H_{31}N$ requires C, 81·0; H, 13·1; N, 5·9%); $n_D^{20°}$ 1·4475; d^{20} 0·8360; $[R_L]_D$ 75·82 (calc., 75·83).

*Methyl β-*n*-amyl-β-*n*-heptylbutyrate* had b. p. 115—117°/0·2 mm. (Found : C, 75·6; H, 12·6. $C_{17}H_{34}O_2$ requires C, 75·6; H, 12·6%); $n_D^{20°}$ 1·4437; $d^{20°}$ 0·8710; $[R_L]_D$ 82·30 (calc., 82·36).

*β-*n*-Amyl-β-*n*-heptylbutyric acid* was obtained as a colourless viscous oil, b. p. 144—149°/0·45 mm. (Found : C, 75·1; H, 12·7; *M*, 255. $C_{16}H_{32}O_2$ requires C, 75·0; H, 12·5%; *M*, 256); $n_D^{20°}$ 1·4526; $d^{20°}$ 0·8904; $[R_L]_D$ 77·65 (calc., 77·62).

*ββ-Di-*n*-heptylbutyric Acid.*—Methyl *n*-heptyl ketone was prepared by the method of Pickard and Kenyon (J., 1911, **99**, 57), b. p. 80—81°/13 mm. ($n_D^{20°}$ 1·4215); semicarbazone, m. p. 119—120°.

Ethyl 1-*methyloctylidenecyanoacetate* was obtained as a pale yellow oil, b. p. 165—168°/13 mm. (Found : C, 70·9; H, 9·7; N, 5·8. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7; N, 5·9%); $n_D^{20°}$ 1·4678; $d^{20°}$ 0·9433; $[R_L]_D$ 69·82 (calc., 67·78; exaltation, 2·04).

The Grignard solution prepared from magnesium (4·5 g.), *n*-heptyl bromide (36 g.), and ether (100 c.c.) was brought into reaction with ethyl methyloctylidenecyanoacetate (30 g.) in the usual way, and yielded *ethyl α-cyano-ββ-di-*n*-heptylbutyrate* (29 g.), b. p. 168—172°/0·5 mm. (Found : C, 74·9; H, 11·6; N, 4·1. $C_{21}H_{39}O_2N$ requires C, 74·8; H, 11·6; N, 4·1%); $n_D^{20°}$ 1·4535; $d^{20°}$ 0·9046; $[R_L]_D$ 100·78 (calc., 100·57). This α-cyano-ester was hydrolysed in the usual way, and *ββ-di-*n*-heptylbutyronitrile* was obtained as a colourless mobile oil, b. p. 145—150°/0·5 mm. (Found : C, 81·3; H, 13·3. $C_{18}H_{35}N$ requires C, 81·5; H, 13·2%); $n_D^{20°}$ 1·4499; $d^{20°}$ 0·8374; $[R_L]_D$ 85·03 (calc., 85·06).

*Methyl ββ-di-*n*-heptylbutyrate* had b. p. 135—140°/0·4 mm. (Found : C, 76·7; H, 12·7. $C_{19}H_{38}O_2$ requires C, 76·5; H, 12·8%); $n_D^{20°}$ 1·4468; $d^{20°}$ 0·8698; $[R_L]_D$ 91·52 (calc., 91·60).

*ββ-Di-*n*-heptylbutyric acid* was obtained as a colourless viscous oil, b. p. 168—172°/0·6 mm. (Found : C, 76·3; H, 12·8. $C_{18}H_{36}O_2$ requires C, 76·1; H, 12·7%); $n_D^{20°}$ 1·4548; $d^{20°}$ 0·8869; $[R_L]_D$ 86·84 (calc., 86·86).

*β-*n*-Propyl-ββ-di*iso*amylpropionic Acid.*—The *iso*amyl iodide used in the following synthesis was prepared from technical *iso*amyl alcohol which contained some active amyl alcohol. The final product had a small optical activity.

n-Propyl *iso*amyl ketone (26 g.), obtained by the action of *n*-butyryl chloride on *iso*amylzinc iodide, was condensed with ethyl cyanoacetate (20 g.) and yielded *ethyl* 1-*n*-*propyliso*hexylidenecyanoacetate (27 g.), b. p. 120—125°/0·4 mm.; $n_D^{20°}$ 1·4679 (Found : C, 70·7; H, 9·7. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7%).

The Grignard solution prepared from magnesium (4·1 g.), *iso*amyl iodide (37 g.), and ether (80 c.c.) reacted with ethyl *n*-propyl*iso*hexylidenecyanoacetate (27 g.) in the usual way. *Ethyl α-cyano-β-*n*-propyl-ββ-di*iso*amylpropionate* was obtained as a colourless oil (24 g.), b. p. 140—145°/0·7 mm.; $n_D^{20°}$ 1·4542 (Found : C, 73·3; H, 11·4. $C_{19}H_{35}O_2N$ requires C, 73·8; H, 11·3%).

The cyano-ester was hydrolysed as usual, and *β-*n*-propyl-ββ-di*iso*amylpropionitrile* obtained as a mobile, colourless oil, b. p. 115—118°/0·8 mm.; $n_D^{20°}$ 1·4479 (Found : C, 80·4; H, 12·8. $C_{16}H_{31}N$ requires C, 81·0; H, 13·1%). *Methyl β-*n*-propyl-ββ-di*iso*amylpropionate* had b. p. 100—108°/0·3 mm.; $n_D^{20°}$ 1·4441 (Found : C, 75·4; H, 12·8. $C_{17}H_{34}O_2$ requires C, 75·6; H, 12·6%). *β-*n*-Propyl-ββ-di*iso*amylpropionic acid* was obtained as a colourless, viscous oil, b. p. 138—145°/0·3 mm.; $n_D^{20°}$ 1·4522 (Found : C, 75·2; H, 12·5. $C_{16}H_{32}O_2$ requires C, 75·0; H, 12·5%). The *amide* separated from light petroleum as greasy plates, m. p. 52—53° (Found : C, 75·2; H, 13·1. $C_{16}H_{33}ON$ requires C, 75·3; H, 12·9%).

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55. 1 : 6-*Diamino* 2 : 3 : 4 : 5-*Dimethylene Mannitol.*

By W. N. Haworth, R. L. Heath, and L. F. Wiggins.

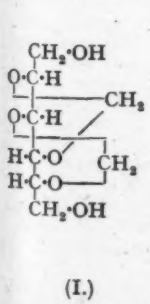
The preparation of 1 : 6-diamino 2 : 3 : 4 : 5-dimethylene mannitol, together with characteristic derivatives, is described. Crystalline salts of the diamine with dibasic acids were obtained. These salts polymerise on heating above their melting points to give polyamides which, however, do not give oriented fibres when cold drawn.

Mannitol was converted into 1 : 6-dichloro mannitol by treatment with fuming hydrochloric acid at 95° under pressure according to the method of Siwoloboff (*Annalen*, 1886, **233**, 368). 1 : 6-*Dichloro dimethylene mannitol* (m. p. 156°) was obtained from 1 : 6-dichloro mannitol either by treatment with 38% formaldehyde solution saturated with hydrogen chloride (Micheel, *Annalen*, 1932, **496**, 77) or by fusion with paraformaldehyde and concentrated sulphuric acid, although the yield by the latter method was inferior.

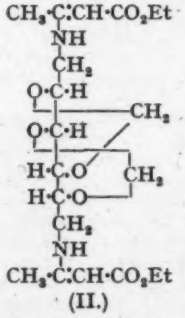
The description of this compound as 1 : 6-dichloro 2 : 3 : 4 : 5-dimethylene mannitol is justified by its formation from 2 : 3 : 4 : 5-dimethylene mannitol (Haworth and Wiggins, this vol., p. 58), since the structure of this compound was proved by these authors and also by the work of Haskins, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 67). In addition, the mother-liquors from the recrystallisation of several batches of dichloro dimethylene mannitol yielded a small amount of an isomeric dichloro dimethylene mannitol (m. p. 96°). 1 : 6-Dichloro dimethylene mannitol (m. p. 156°) on treatment with a large excess of methyl-alcoholic ammonia (saturated at 0°) in an autoclave at 150° for 72 hours was converted into crystalline 1 : 6-*diamino* 2 : 3 : 4 : 5-*dimethylene mannitol dihydrochloride*, from which crystalline 1 : 6-*diamino dimethylene mannitol* or its *hydrate* was isolated by treatment with a slight excess of barium hydroxide. The distilled diamine was obtained in 60% of the theoretical yield from dichloro dimethylene mannitol. Secondary and tertiary amino-products were not encountered. Greatly diminished yields resulted if the concentration of dichloro dimethylene mannitol in the methyl-alcoholic ammonia exceeded 3% or if the reaction temperature was very much lower than 150°. Under these conditions extensive and sometimes violent polymerisation often accompanies distillation of the product, and only small amounts of diamino dimethylene mannitol distil. Probably this is caused by the elimination of the elements of hydrogen chloride between some unchanged dichloro dimethylene mannitol and the diamino dimethylene mannitol, with the formation of secondary amino-linkages. 1 : 6-*Diphthalimido dimethylene mannitol* was obtained from 1 : 6-dichloro dimethylene mannitol, although in poor yield, and gave, by means of Ing and Manske's hydrazine method of hydrolysis (J., 1926, 2348), the crystalline 1 : 6-diamino dimethylene mannitol.

The orientation of the methylene groups in these compounds is at present in doubt. The isolation of two isomeric dichloro dimethylene mannitols from the same 1 : 6-dichloro mannitol can only be accounted for by different orientation of the methylene groups. Obviously there are the same three possible structures for dichloro dimethylene mannitol and diamino dimethylene mannitol as for dimethylene mannitol itself (Haworth and Wiggins, *loc. cit.*), since the methylene groups may bridge (*a*) C_2 and C_4, C_3 and C_5; (*b*) C_2 and C_3, C_4 and C_5; and (*c*) C_2 and C_5, C_3 and C_4. We are not yet able to state which of the three possibilities corresponds to each of the isomers actually isolated. The structures (*a*) and (*c*) will possess a rigidity which is not shown by (*b*), since free rotation about the C_3–C_4 bond is possible in this structure. From the point of view of the formation of linear polymers, a structure of the diamino dimethylene mannitol based on either (*a*) or (*c*) is more favourable, since in these the carbon chain must be extended and rigid, whereas in (*b*), where the methylene groups are attached to adjacent carbon atoms, this is not the case. The formula (I) shows the first of these possibilities, which has some support from the following facts: we have obtained the dimethylenetetrahydroxy-$\Delta^{1:5}$-hexadiene of Micheel (*loc. cit.*) in excellent yield by the action of alcoholic potash or of sodium on 1 : 6-dichloro dimethylene mannitol (m. p. 156°); the difficulty which Micheel (*loc. cit.*) found in cyclising derivatives of dimethylene mannitol to dimethylene cyclitol. A study of models of (I) shows that the methylene groups are so arranged that the addenda on C_1 and C_6 are relatively far apart.

The 1 : 6-diamino dimethylene mannitol gave a number of well-crystallised derivatives. A Schiff's *base* with salicylaldehyde, a *di*-p-*nitrobenzenesulphonyl* derivative, and also a dipicrate were obtained. 1 : 6-Diamino dimethylene mannitol was also converted by fusion with phthalic anhydride in 50% yield into 1 : 6-diphthalimido dimethylene mannitol, identical with that obtained by the reaction between dichloro dimethylene mannitol and potassium phthalimide. Furthermore, the diamine gave a crystalline *compound*, $C_{20}H_{32}O_8N_2$, on treatment with ethyl acetoacetate in the presence of a trace of hydrogen chloride. This derivative may have the structure represented by (II).



(I.)



(II.)

Crystalline *salts* were also obtained with such dibasic acids as oxalic, adipic, and sebacic acid. Attempts were made to prepare salts of the diamine with the dimethylene glucosaccharic acid and its epimeride dimethylene *l*-idosaccharic acid (Haworth, Jones, Stacey, and Wiggins, this vol., p. 61); the former did not yield a solid compound, but the latter gave a very fine crystalline salt. Tetramethyl glucosaccharic acid also failed to form a crystalline salt with the diamine.

Polymerisation of the crystalline salts was carried out by heating in a vacuum or in sealed tubes in an

atmosphere of nitrogen. In every case, however, serious darkening of the product occurred, and, moreover, the fibres which could be drawn from the cooling melt were brittle and did not exhibit the property of "cold drawing" which is characteristic of the Nylon fibres.

The methylene groups in 1 : 6-diamino dimethylene mannitol were exceedingly stable towards acids. Boiling with 5% hydrochloric acid did not effect hydrolysis. Long boiling with 10% hydrochloric acid, however, removed the methylene groups and in this way crystalline 1 : 6-*diamino mannitol dihydrochloride* was obtained.

Experimental.

1 : 6-*Dichloro Mannitol.*—Mannitol (50 g.) was mixed with 300 c.c. of fuming hydrochloric acid, which was prepared by passing hydrogen chloride into concentrated hydrochloric acid cooled to 0° until it was saturated, and the resulting solution poured into a Pyrex-glass tube of 500 c.c. capacity, and the tube immediately sealed off. Ten such tubes were prepared and placed upright in a large water-bath so that at least the liquid inside the tubes was immersed in the water. The tubes rested on a wire-gauze tray fixed $\frac{3}{4}$" from the bottom of the water-bath. A cover was placed over the tubes and they were heated at 90—95° for 36 hours. When the tubes had cooled, they were opened in the usual way. On rare occasions the end of the tube was blown off during this opening process but never with any great force. The contents of the tubes were poured into a large bolt-head flask, and evaporated to dryness in a vacuum below 50°. The residue, a semi-crystalline mass, was taken up in 800 c.c. of water and evaporated to dryness again; if this was repeated once more, there was very little hydrogen chloride left in the product. The semi-crystalline residue was taken up in 1 l. of water, heated on the boiling water-bath for 5 minutes with charcoal, and filtered hot, the filtrate being evaporated in a vacuum to crystallising point, whereupon the liquid was poured into a conical flask and allowed to crystallise at 0°. The crystals were collected after 24 hours, and washed with a little ice-water and alcohol. Yield, 120 g.; m. p. 174°. The mother-liquors were again saturated at 0° with hydrogen chloride, and the liquid distributed equally amongst ten tubes, each being made up to 300 c.c. with fuming hydrochloric acid. The tubes were sealed and heated under the same conditions as before, and the product isolated in the same way. Yield of crystals, 60 g.; m. p. 174°. Total yield, 180 g.; 30% of the theoretical. In some preparations yields of 40% were obtained.

The residues after these two treatments with hydrochloric acid have not been fully investigated, but give on distillation a liquid which contains some 1 : 4—3 : 6-dianhydromannitol and some 2-chloro dianhydromannitol, and some partly chlorinated monoanhydro-compounds. A full account will be published later.

1 : 6-*Dichloro Dimethylene Mannitol.*—1 : 6-Dichloro mannitol (100 g.) was suspended in 40% formalin solution (250 c.c.), and the mixture cooled in ice. Hydrogen chloride was passed in with constant shaking until a saturated solution was obtained; the dichloro mannitol dissolved, and a precipitate separated together with an oily polymer of formaldehyde. On keeping overnight at 0° crystallisation was complete, and after dilution with water the product was collected and washed with water. Recrystallised from alcohol, it formed large, thick needles (80 g.), m. p. 156°. The mother-liquors from the recrystallisation of several batches were combined, and after separation of a little more 1 : 6-dichloro dimethylene mannitol, m. p. 156°, a very small amount of feathery needles separated, m. p. 96°, $[\alpha]_D$ −18·2° (Found : C, 39·4; H, 5·2; Cl, 28·1. $C_8H_{12}O_4Cl_2$ requires C, 39·5; H, 5·0; Cl, 29·2%). This substance was an isomeric *dichloro dimethylene mannitol.*

An alternative method of preparation was tried. Dichloro mannitol (20 g.) was ground with paraformaldehyde (20 g.) and stirred with 13 c.c. of concentrated sulphuric acid. The mixture warmed to about 60° and was stirred occasionally until it cooled again. It was then shaken for 3 hours with 200 c.c. of chloroform, the chloroform poured off, another 200 c.c. added, and the mixture shaken for a further hour. The combined chloroform extracts were washed with dilute aqueous ammonia and with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. The residue was crystallised from alcohol. Yield, 13 g. (60%); m. p. 155—156°.

1 : 6-*Diphthalimido Dimethylene Mannitol.*—1 : 6-Dichloro dimethylene mannitol (2 g.) was intimately mixed with potassium phthalimide (4 g.) and heated to 200°; when a few drops of glycerol were added, the mass became semi-liquid (without the addition of glycerol no fusion occurred). Heating was continued for 3 hours at 160—170°. When cold, the mass was extracted twice with boiling water, and the residue dried and recrystallised from chloroform–petrol; m. p. 277°. Yield, 0·7 g. (20%) (Found : C, 61·9; H, 3·9; N, 6·8. $C_{24}H_{20}O_6N_2$ requires C, 61·8; H, 4·2; N, 6·2%).

1 : 6-*Diamino Dimethylene Mannitol from the Diphthalimide Derivative.*—1 : 6-Diphthalimido dimethylene mannitol (0·45 g.), suspended in 25 c.c. of absolute alcohol and boiled with hydrazine hydrate (2 c.c.), dissolved after $\frac{1}{2}$ hour; after a further $\frac{1}{2}$ hour the alcohol was removed under diminished pressure. The residue was dissolved in 5 c.c. of water, N-hydrochloric acid added until the solution was acid to Congo-red paper, the mixture heated for 5 minutes at 100°, and the precipitate of phthalhydrazide removed. The filtrate was made alkaline with N-sodium hydroxide and evaporated to dryness. The dry residue was extracted several times with boiling chloroform, and the extracts dried and evaporated. Yield of syrup, which rapidly crystallised on cooling, 0·13 g. This was recrystallised from ethyl acetate–ether; m. p. 48—52°. A mixed m. p. with the diamino dimethylene mannitol obtained by the action of methyl-alcoholic ammonia on 1 : 6-dichloro dimethylene mannitol showed no depression.

1 : 6-*Diamino Dimethylene Mannitol.*—1 : 6-Dichloro dimethylene mannitol (30 g.) was suspended in 1 l. of methyl-alcoholic ammonia (saturated at 0°) and heated in an autoclave at 145—150° for 3 days. The brown solution was evaporated to dryness in a vacuum until all the ammonia had disappeared. Barium hydroxide (40 g.), dissolved in 300 c.c. of hot water, was added, and the mixture heated for 1 hour in a stream of nitrogen. The water was evaporated, and the residue dried at 100° in a vacuum vessel, an atmosphere of nitrogen being present. The residue was extracted 6 times with 250-c.c. portions of chloroform under reflux, and the extracts evaporated to a syrup; this distilled under high vacuum as a yellow oil which crystallised completely. Yield, 15 g. (60%). All the latter operations were conducted in an atmosphere of nitrogen.

1 : 6-*Diamino* 2 : 3 : 4 : 5-*Dimethylene Mannitol Dihydrochloride.*—1 : 6-Diamino dimethylene mannitol (13 g.) (distilled product) was dissolved in water (30 c.c.), and concentrated hydrochloric acid (15 c.c.) added at 0°. Alcohol was then added until a slight turbidity had developed; crystallisation took place rapidly. Yield, 15·5 g. (90%); m. p. 220—224° (decomp.) (Found : C, 34·3; H, 6·3; N, 11·0; Cl, 25·7. $C_8H_{18}O_4N_2Cl_2$ requires C, 34·7; H, 6·5; N, 10·1; Cl, 25·6%).

Conversion of 1 : 6-*Diamino Dimethylene Mannitol Dihydrochloride into* 1 : 6-*Diamino Dimethylene Mannitol.*—The dihydrochloride (13 g.) was dissolved in 50 c.c. of water, a solution of 16 g. barium hydroxide in 100 c.c. of hot water added, and the mixture heated at 100° for 1 hour in a stream of nitrogen. Evaporation to dryness and extraction with chloroform (6 times under reflux) gave a light yellow syrup (9 g.) which crystallised to a solid mass on cooling. Recrystallisation was effected from dioxan–ether. Yield, 8 g. (83%); m. p. 48—52°. The product was colourless but very hygroscopic and was apparently a *monohydrate*; $[\alpha]_D^{18°}$ +67·7° ($CHCl_3$; *c*, 2·48) (Found : C, 43·8; H, 7·9; N, 12·5; H_2O, 6·1. $C_8H_{18}O_4N_2.H_2O$ requires C, 43·2; H, 7·9; N, 12·7; H_2O, 8·1%). The anhydrous *diamine*, m. p. 50°, could be

obtained by recrystallisation from dry ethyl acetate–ether (Found : C, 47·4; H, 8·1; N, 12·0. $C_8H_{16}O_4N_2$ requires C, 47·1; H, 7·8; N, 13·7%).

1 : 6-*Bis*-N-*salicylideneamino Dimethylene Mannitol.*—1 : 6-Diamino dimethylene mannitol (0·2 g.) was dissolved in a few c.c of water containing a drop of N-sodium hydroxide. Salicylaldehyde (0·23 g.) was added, and the mixture vigorously shaken for an hour. The yellow solid which had separated was collected, washed with water, and recrystallised from alcohol–acetone, forming yellow plates (0·28 g.), m. p. 191—192° (Found : C, 64·1; H, 5·5; N, 6·8. $C_{22}H_{24}O_4N_2$ requires C, 63·8; H, 5·5; N, 6·4%).

Salts of 1 : 6-*Diamino Dimethylene Mannitol.*—*Oxalate.* The diamine (0·1 g.) was dissolved in absolute alcohol, and 0·05 g. of oxalic acid, also dissolved in alcohol, added; a fine granular precipitate then separated. An equal volume of water was added, and the alcohol boiled off until a clear solution was obtained. Crystals separated on cooling (0·06 g.), m. p. 280° (decomp.) (Found : C, 41·2; H, 6·3; N, 10·3. $C_8H_{16}O_4N_2,H_2C_2O_4$ requires C, 40·8; H, 6·1; N, 9·5%).

Dimethylene l-*idosaccharate.* A solution of the diamine (0·1 g.) in alcohol was added to dimethylene *l*-idosaccharic acid (0·1 g.), also dissolved in alcohol; a granular precipitate separated. This was treated as for the oxalate, feathery needles of the *salt* separating (0·16 g.); it decomposed slowly between 270° and 300° (Found : C, 43·9; H, 6·0; N, 6·2. $C_8H_{16}O_4N_2,C_6H_{10}O_8$ requires C, 43·8; H, 5·9; N, 6·4%). An attempt to prepare a salt with dimethylene glucosaccharic acid failed to produce any crystals.

Adipate. The diamine (0·1 g.) was dissolved in alcohol, and an alcoholic solution of adipic acid (0·07 g.) added; a granular precipitate formed. On being worked up as before, this *adipate* separated in small needles (0·08 g.), m. p. 205° (Found : C, 48·2; H, 7·4; N, 8·5. $C_8H_{16}O_4N_2,C_6H_{10}O_4$ requires C, 48·0; H, 7·4; N, 8·0%).

Sebacate. 1 : 6-Diamino dimethylene mannitol (0·1 g.), dissolved in alcohol, was added to sebacic acid (0·1 g.) dissolved in alcohol–water. The mixture was boiled until clear, and alcohol added until the solution was just turbid. Long feathery needles separated (0·12 g.), m. p. (after drying at 100°) 162° (Found : C, 52·8; H, 8·6; N, 6·5. $C_8H_{16}O_4N_2,C_{10}H_{18}O_4$ requires C, 53·1; H, 8·4; N, 6·9%).

Polymerisation.—(*a*) 1 : 6-Diamino dimethylene mannitol adipate (0·5 g.) was heated in a vacuum. A fine capillary tube through which nitrogen was passing was immersed in the salt, which was heated a little above its m. p., *i.e.*, at 210—215°. The melt, however, darkened appreciably to a red-brown. After 3 hours the melt on cooling set to a hard resin, and if a glass rod was dipped into the cooling mass, long fibres could be drawn out and wound round a test tube. These light yellow fibres were highly lustrous but brittle. They could not be " cold drawn."

(*b*) The corresponding sebacate was heated in a sealed tube, in which the air had been replaced by nitrogen, immersed in an oil-bath at 170° for 4 hours. The melt thickened appreciably, and after the tube had been cooled and opened, the melt, on warming, could be drawn into light brown fibres; these, however, were brittle and could not be cold drawn. The tube was resealed, and the contents heated again, in an atmosphere of nitrogen at 250° for a further 4 hours. The product, however, darkened still more, became an elastic gel, and resinified on cooling, and fibres could not satisfactorily be drawn from it.

1 : 6-*Bis*-p-*nitrobenzenesulphonamido Dimethylene Mannitol.*—1 : 6-Diamino dimethylene mannitol (0·5 g.) was dissolved in dry pyridine, *p*-nitrobenzenesulphonyl chloride (1 g.) added, and the mixture kept at room temperature for several days. The solution assumed a deep orange colour and crystals separated. When it was poured into ice-water, a solid separated. After being washed with water, this was recrystallised from acetone–water, forming small crystals (1·1 g.), m. p. 249—251° (Found : C, 41·9; H, 3·9; N, 10·1. $C_{20}H_{22}O_{12}N_4S_2$ requires C, 41·8; H, 3·8; N, 9·7%).

Condensation of 1 : 6-*Diamino Dimethylene Mannitol with Phthalic Anhydride.*—The diamine (1 g.) was mixed with phthalic anhydride (1·4 g.) and heated at 160° for 2 hours. Some frothing occurred at 130°, and after about ½ hour's heating the melt hardened appreciably. After cooling, the mixture was ground and extracted with boiling chloroform, the extract filtered (charcoal) and evaporated to dryness, and the residue extracted with boiling water. The residual mass was dried, and recrystallised from chloroform–petrol. Yield, 1·1 g. (50%); m. p. 277°, not depressed by the product of reaction between 1 : 6-dichloro dimethylene mannitol and potassium phthalimide.

Condensation of 1 : 6-*Diamino Dimethylene Mannitol with Ethyl Acetoacetate.*—The diamine (0·2 g.) was mixed with the ester (3 c.c.), and 1 drop of concentrated hydrochloric acid added. The mixture was shaken occasionally for 12 hours, a little ether added, and the mixture left overnight; the crystals which separated were filtered off and recrystallised from alcohol, forming colourless prisms, m. p. 120°, $[\alpha]_D^{15°}$ +67·2° (*c*, 2·62 in chloroform) (Found : C, 56·6; H, 7·4; N, 6·3. $C_{20}H_{32}O_8N_2$ requires C, 56·1; H, 7·5; N, 6·5%). The *compound* was soluble in chloroform and alcohol but insoluble in water.

1 : 6-*Diamino Mannitol Dihydrochloride.*—(*a*) 1·3 G. of 1 : 6-diamino dimethylene mannitol dihydrochloride were dissolved in 50 c.c. of 5% hydrochloric acid and boiled for 12 hours. Evaporation gave a crystalline mass which, recrystallised from alcohol–water, formed prisms, m. p. 217—220° (decomp.); mixed m. p. with the original material gave no depression (Found : C, 34·4; H, 6·9; N, 10·4. Calc. for $C_8H_{16}O_4N_2,2HCl$: C, 34·7; H, 6·5; N, 10·1%). Therefore no hydrolysis of the methylene groups had taken place under these conditions.

(*b*) The dihydrochloride as in (*a*) (1 g.) was heated with 100 c.c. of 10% hydrochloric acid for 16 hours. Evaporation gave a solid residue, which was recrystallised from alcohol–water. Yield, 0·5 g.; m. p. 238—240° (decomp. at 302—305°) (Found : C, 28·5; H, 7·0; N, 11·6; Cl, 28·5. $C_8H_{16}O_4N_2,2HCl$ requires C, 28·4; H, 7·1; N, 11·1; Cl, 28·1%).

Dimethylenetetrahydroxy-$\Delta^{1:5}$*-hexadiene.*—This substance was first prepared by Micheel (*loc. cit*) and the following are improvements on his method:

(*a*) 1 : 6-Dichloro dimethylene mannitol (5 g.) was dissolved in 2N-alcoholic potassium hydroxide (100 c.c.) and refluxed for 4 hours. After neutralisation with 2N-hydrochloric acid and separation of the precipitated potassium chloride, the filtrate was evaporated to dryness. Extraction of the residue with ether gave, after removal of the ether, a thin syrup which rapidly crystallised. Recrystallisation from ether–petrol (b. p. 40—60°) gave dimethylenetetrahydroxy-$\Delta^{1:5}$-hexadiene in 91% of the theoretical yield, m. p. 80°.

(*b*) 1 : 6-Dichloro dimethylene mannitol (10 g.) was melted and kept at 160° while sodium wire (2·4 g.) was slowly added. The vigorous reaction which took place initially necessitated the removal of the external source of heat until most of the sodium had been added and the reaction mixture had become solid owing to the separation of sodium chloride. Dry toluene (30 c.c.) was added, and the mixture heated for 2 hours under reflux. The clear, supernatant liquid was decanted, and two further extractions made. The combined toluene extracts were filtered and evaporated, a mobile liquid being obtained which crystallised rapidly on cooling. After recrystallisation from benzene–light petroleum, dimethylenetetrahydroxy-$\Delta^{1:5}$-hexadiene separated, m. p. 80°. Yield, 5·6 g. (85%); $[\alpha]_D^{20°}$ +281·5° ($CHCl_3$). Micheel (*loc. cit.*) gives m. p. 80°, $[\alpha]_D^{20°}$ +280° ($CHCl_3$).

The authors are indebted to I.C.I. (Dyestuffs) Ltd. for a grant in aid of this work.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

[*Received, December 23rd,* 1943.]

THE HUNDRED AND THIRD ANNIVERSARY MEETING.

THE Annual General Meeting was held at Burlington House on Thursday, 20th April, 1944, at 11.30 a.m., the President, Dr. W. H. Mills, F.R.S., occupying the Chair.

The notice convening the meeting was read.

The Report of Council for 1943, copies of which were available at the meeting, was presented, and Dr. C. W. Davies, in introducing the Report, referred to the privileges afforded to Students by the scheme of Joint Junior and Joint Student Membership and appealed to senior Fellows to co-operate by drawing the attention of their students to the scheme. He referred to the steps indicated in the Report to improve the balance of the *Annual Reports*, and to the gradual decline in the proportion of physico-chemical papers in the *Journal*. He stated that it would be a tragedy if the *Journal*, with its long tradition, ceased to be fully representative of British Chemistry, and asked physical Chemists to collaborate by submitting papers for publication in the *Journal*. He also drew attention to the important matters of policy discussed in the Reports of the Bureau and the Joint Library Committee appearing as appendixes.

In conclusion, he said that every year of war added to the complexities and difficulties of the activities of the Society, and paid tribute to the work of the General Secretary and his staff.

The Treasurer referred to the work of the conjoint office, to which members of the Chemical Society's staff were seconded, and to the work of the Library Staff. Without the conjoint office the co-operation scheme would be difficult to work, and Mr. Morris, who is in charge of that office with Miss Knight as his second, had, in spite of difficulties due to inadequate staff, done splendid work. The Annual Meeting was held in April, as with the complexities caused by the co-operation scheme it was not possible to have the accounts ready in time for a March Meeting, and, indeed, he doubted if it would be in peace time. The preparation of the accounts coincided with the time when the subscriptions were coming in, with many changes in the choice of publications, and consequent necessity for assistance to the staff engaged on the distribution of publications.

Cost of Publications to Joint Members, 1942.

Publication.	No. of copies printed.	Total net production cost.	Cost per copy per annum.	No. of copies supplied to Joint Members.	Cost of publications supplied to Joint Members. Chem. Soc.	Bureau.
		£	s. d.		£	£
Journal	4450	4835	21 9	1209	1315	—
A I	2702	1852	13 8	589	403	—
A II	2691	1887	14 0	717	502	—
A III (Total)	2631	3103	23 7	396	—	—
(Bureau)	—	1603	12 2	—	—	240
(C.S.)	—	1500†	11 5	—	225	—
A Index (Total)	3300	1307	7 11	632	—	—
A III (Bureau) ...	—	730	4 5	—	—	140
A I and A II (C.S.) ...	—	577	3 6	—	116	—
Lecture Reprints	700	60	1 9	587	51	—
Annual Reports	4000	958	4 9	1444	343	—
				Total net cost	2955	380

	£	£		£
§Receipts from Joint Members		4363	§ Cost of Publications to S.C.I.	3347
Less Society of Chemical Industry	196 §		,, ,, ,, C.S..	2955
Cost of Publications	2955			
		3151	Difference	£392
Balance		£1212		

§ As the money received from co-operation members is, after deduction of any subscription to the Royal Institute of Chemistry, divided equally between the Chemical Society and the Society of Chemical Industry, an adjustment is necessary each year so that the two Societies benefit equally after allowing for cost of publications.

† £1500 per annum is the agreed contribution of the Chemical Society to A III.

He stated that the number of Fellows, 5232, and the amount received from subscriptions, £11,068, was a record, and that there seemed no reason to think that further increases would not be shown as the benefits of the co-operation scheme were more and more appreciated.

It had been asked if the Society benefited financially from the Co-operation Scheme. The table on p. 158 shows that in 1942, after defraying costs of publications supplied and making due allowance for overheads, there was a surplus of £1212 towards the general expenses of the Society from this source.

He then directed attention to the Special Reserve Fund, which now stood at £13,938. This would be of substantial assistance after the war, but he doubted if it would prove sufficient to meet the cost of the increased number of original papers and abstracts to be published in the post-war years, as well as that of reprinting many of the war-time issues of the *Journal* and *Abstracts* which would be required for Fellows who had not received them while on duty in the Forces, as well as for supplying foreign countries. The paper ration had been insufficient to make full provision for this.

Finally, he dealt briefly with the salient features of the Accounts.

The adoption of the Report of Council for 1943, including Statement of Accounts and Balance Sheets, was proposed by Mr. R. P. Bell, seconded by Dr. James Bell, and carried unanimously.

The names of Fellows elected to vacancies on the Council for 1944—1945 were declared as follows:

President:

Professor W. N. Haworth.

Vice-President, who has not filled the office of President:

Mr. E. J. Bowen.

The report of the Scrutators on the ballot for Elected Ordinary Members of Council for Constituencies I and IV was read, and it was declared that the following had been elected:

Constituency I (South-East England):

Dr. M. P. Balfe, Dr. E. R. H. Jones, and Professor W. F. K. Wynne-Jones.

Constituency IV (North-East England):

Dr. M. P. Applebey and Dr. L. Hunter.

A vote of thanks to the Vice-Presidents, Treasurer, Honorary Secretaries, Council and Committees for their services during the past year, proposed by Dr. J. Kenyon, and seconded by Dr. R. Fraser Thomson, was carried, and acknowledged by Sir John J. Fox.

On the motion of Dr. G. H. Christie, seconded by Dr. Brynmor Jones, Messrs. W. B. Keen & Co., were appointed Auditors to audit the accounts of the Society for 1944.

The meeting was then adjourned.

A luncheon attended by Fellows was held at Stewarts Restaurant (Old Bond Street) at 1 p.m.

The meeting was resumed at 2.30 p.m., and Dr. W. H. Mills delivered his Presidential Address, entitled "Old and New Views on some Chemical Problems." At the conclusion, a vote of thanks to him for his services in the Chair during his term of office and for his Address, with the request that he would allow his Address to be printed in the *Journal*, was proposed by Dr. F. H. Carr, seconded by Dr. J. W. Baker, and carried with acclamation. The President acknowledged the vote of thanks and referred to the loyal support he had received from the Officers and Council.

Professor W. N. Haworth, who was then inducted into the Chair, expressed his appreciation of the high honour conferred on him, and declared the meeting closed.

REPORT OF COUNCIL, 1943.

The year 1943 saw the collaboration between the Chartered chemical bodies taken a stage further in the adoption of the Chemical Council's scheme of Joint Junior and Joint Student Membership. This scheme is proving attractive to young chemists and will have the effect of making known to them the various services rendered by the three chartered bodies to the chemical community. Senior Fellows are asked to co-operate by drawing the attention of students to its provisions.

I. FELLOWSHIP.

(1) *Fellowship Statistics.* The number of Fellows on the 31st December, 1942, was 4826. During 1943, 543 Fellows were elected and 31 reinstated, the corresponding figures in 1942 being 475 and 29, respectively. The Society has lost 2 Fellows killed in action, 58 by death, 42 by resignation and 66 by removal for non-payment of annual subscription—a total loss of 168 compared with 194 in 1942. The number of Fellows on the 31st December, 1943, was 5232; of these, 1885 are joint members of the three

Chartered Bodies, and 565 of the two Publishing Societies. Of the joint members of the three bodies elected in 1943, 192 are new Fellows of the Chemical Society and of the joint two-body members, 75 are new Fellows. The number of joint members of the three Chartered Bodies has increased during the year by 238, of the two Publishing Societies by 107, and of single-body Fellows by 61.

On 15th April, the Council elected Professor Linus Pauling (Pasadena), Professor Nikolai Semenov (U.S.S.R.) and Professor Nikolai Zelinsky (U.S.S.R.) Honorary Fellows of the Society. The number of Honorary Fellows is now 27.

(2) 60 *and* 50 *Years of Fellowship.* During the year the congratulations of the Society have been conveyed to 8 Fellows who had completed 60 years of Fellowship, and to 20 who had completed 50 years of Fellowship. Their names have appeared in the Proceedings.

(3) *Deaths.* The Council mourn the loss of Professor Fred Swarts, who was elected an Honorary Fellow of the Society in May, 1931. Among prominent Fellows of the Society whose deaths the Council have to record are Professor P. P. Bedson, Mr. W. R. Bousfield, Dr. G. T. Moody, Dr. H. Forster Morley and Dr. S. Ruhemann, each of whom had served on the Council. Pilot Officer C. R. Morrison-Jones, R.A.F.V.R. and Pilot Officer E. A. Wagstaff, R.A.F.V.R. lost their lives while on Active Service.

II. PUBLICATIONS.

(1) *Journal.* During the year 208 papers were received by the Society; of these 3 were declined.

The *Journal* for 1943, occupying 662 pages, contains 175 memoirs (37 on General, Physical, and Inorganic Chemistry, and 138 on Organic Chemistry), 14 notes, and 3 lectures (18 pages), in addition to Obituary Notices (25 pages) and the report of the Annual General Meeting (24 pages). The corresponding figures for 1942 are 758 pages, 167 memoirs, 21 notes, and 7 lectures.

The Council have again given anxious consideration to the low proportion of physico-chemical papers in the *Journal.* Physical chemists take a full share in the other activities of the Society, and are well represented on the Publication Committee; yet the *Journal* seems in growing danger of becoming preponderatingly organic in character, at least as regards the original work communicated. It has been suggested that the diversion of much physico-chemical work to other journals has been due partly to an idea that theoretical work is not welcome in the *Journal,* and partly to an unduly restrictive publication policy. Whatever grounds there may have been in the past for these views, the Council are resolved that the *Journal* should be as suitable a medium as any other for the publication of physico-chemical work, and will welcome suggestions having this object in view.

(2) *Abstracts.* The report of the Bureau appears as Appendix A.

(3) *Annual Reports.* Volume XXXIX (1942) of the *Annual Reports on the Progress of Chemistry* contained 255 pages, as against 297 pages in Volume XXXVIII for 1941. It is regretted that owing to war conditions the volume for 1942 did not appear until August; also that it was found necessary to omit Sections on Analytical Chemistry and Radioactivity, and to curtail others, and that sufficient copies were not available to meet the demands even of Fellows. It is intended to reprint this volume when paper is available. The prospects for the Annual Reports for 1943 are better.

Council has adopted recommendations of the Publication Committee (1) to discontinue the separate Report on Crystallography, enlarging the scope and size of the Report on General and Physical Chemistry to include crystallographical work of chemical interest; and (2) to discontinue separate Annual Reports on Radioactivity and Sub-Atomic Phenomena, but to include in other sections matters of chemical interest arising out of the subject and further to publish separate Reports on Radioactivity whenever a general review of that subject seems opportune. Effect will be given to these changes in Volume XLI.

(4) *Volume on "British Chemists."* Council have decided to proceed with the preparation of a volume of articles on representative British Chemists, to supplement the volumes of Memorial Lectures describing the work of foreign chemists, and have been fortunate in securing as Editors Professor Alex. Findlay and Dr. W. H. Mills. It is hoped to publish the volume at the time of the Centenary Celebrations.

III. MEETINGS.

(1) *Scientific Meetings.* During 1943 six meetings were held in London and thirty outside London. A list of these is given in Appendix C.

(2) *Annual General Meeting.* The Hundred and Second Annual General Meeting was held in London on the 25th March, and a full report was published in the *Journal* for April.

Owing to the difficulties in presenting the accounts of the Society in time for an Annual General Meeting in March, power has been obtained from the Privy Council to vary Bye-Law 69 as a war time measure, so as to permit the Annual General Meeting to be held in April.

IV. LIBRARY.

The Annual Report of the Joint Library Committee for 1943 appears as Appendix B.

V. ADMINISTRATION.

Local Representatives and Representatives Overseas. The resignations of Dr. T. S. Stevens and Dr. A. W. Chapman from the offices of Local Representative for Glasgow and Sheffield, respectively, were received with regret; Dr. James Bell and Dr. Brynmor Jones were appointed to fill the two vacancies.

The Council have had under consideration the question of appointing further Representatives to look after the interests of the Society overseas, and are happy to record that the following Fellows have agreed to act in this capacity :—

Canada : Professor W. D. McFarlane (St. Anne de Bellevue).
India : Sir Shanti S. Bhatnagar (Lahore).
New Zealand : Professor F. G. Soper (Dunedin).
South Africa : Professor William Pugh (Rondebosch).

Accommodation. The urgent need of adequate accommodation for administrative work, library purposes, and scientific meetings has again engaged the earnest attention of the Council. Following Sir Henry Dale's Presidential Address to Fellows of the Royal Society on 30th November, when he dealt with the necessity for further accommodation for the Learned Societies resident in Burlington House, the President supported this claim for recognition by His Majesty's Government of the needs of science by writing to *The Times* pointing out the desperate position of the Chemical Society as regards accommodation. This matter is being actively pursued.

Joint Junior and Joint Student Membership. Proposals for Joint Junior and Joint Student Membership received from the Chemical Council were unanimously adopted; full details of the scheme were circulated to Fellows in the autumn, and were also embodied in a brochure dealing with the activities of the three Chartered Chemical Bodies drawn up by the Chemical Council and widely circulated. The Privy Council has granted permission to vary temporarily Bye-Law 8 (c), thus permitting the Society to accept from Student Members subscriptions of less than one-half the full Annual Subscription.

VI. FINANCE.

Collection of Annual Subscriptions from Fellows in Australia and New Zealand. To meet the convenience of Fellows residing in Australia and New Zealand, the Society has opened an account with the Commercial Bank of Australia, Ltd., so that all payments to and from the Society may be made through that account as from the beginning of 1944.

Advertisements. From the beginning of 1944, all arrangements in connection with advertisements in the *Journal* and *Annual Reports* will be undertaken by the Advertisement Department of the Society of Chemical Industry, which is already responsible for advertisements in the Abstracts. This renders it necessary to terminate the contract with Messrs. Walter Judd Ltd., who have for many years acted as the Society's Advertisement Agents to the complete satisfaction of the Council.

Insurances. Fire and war damage insurances on the Library and on Publications have been increased by £250 and £750, respectively.

Investments. The following investments have been made during the year :—

£1650 Special Reserve Fund for publications in National War Bonds, 2½ per cent., 1945—1947.
£150 Staff Pensions Fund in National War Bonds 2½ per cent., 1951—1953.
£100 Life Composition Fees in 3 per cent. Savings Bonds, 1960—1970.
£1100, the proceeds of the surrender of £1096 6*s.* 2*d.* Union of South Africa 3 per cent. stock in 3 per cent. Savings Bonds, 1960—1970.
£807 P. & O. Steam Navigation Co. Deferred Stock was sold and the proceeds were invested in 3 per cent. Savings Bonds, 1960—1970.

Printing Charges. The charges for printing have been increased by a further 7½ per cent. as from the 1st December, 1943.

Contributions. The Council have received £1050 from the Chemical Council; also contributions of £500 from the Rockefeller Foundation, and £200 from the Government Grant, have been made by the Royal Society. The Council again record their thanks for this valuable financial aid towards the cost of the Society's publications for 1943 and to those Fellows who continue to contribute to the Publications Fund. They desire in particular to acknowledge the generous gift of £60 from Mr. T. R. Cowie to mark the completion of his 60 years of Fellowship.

VII. ACKNOWLEDGMENTS.

The Council have recorded their gratitude to the many Fellows who have continued to give their services freely to the Society during the year, and to the Royal Academy for housing publications of the Society previously stored with the printers.

INCOME AND EXPENDITURE GENERAL PURPOSES ACCOUNT FOR THE YEAR ENDED 31ST DECEMBER, 1943.

1942 £ s. d.	1942 £ s. d.	*Income.*	1943 £ s. d.	1943 £ s. d.
	23 10 6	To Life Composition Fees (£135 0s. 0d.), one-third as Income		45 0 0
		„ Annual Subscriptions:		
		Single-body Fellows—		
191 4 2		Received in advance, on account of 1943	1,165 12 3	
4,997 7 4		Received during 1943 on account of 1943	4,475 14 6	
567 8 8		Received during 1943 on account of 1942	364 11 6	
30 0 0		Received during 1943 on account of 1941 and previous years	76 1 6	
		Joint Fellows—		
26 2 6		Received in advance on account of 1943	460 10 3	
4,336 18 8		Received on account of 1943	4,622 9 4	
28 14 3		Received during 1943 on account of 1942 and previous years	67 4 10	
10,177 15 7			11,232 4 2	
		Less Adjustment for publications supplied to co-operation members —Society of Chemical Industry...	163 10 0	
249 0 0				
9,928 15 7			11,068 14 2	
		Less Amount included in last year's Income, being valuation of Arrears as per last Balance Sheet	350 0 0	
250 0 0				
9,678 15 7			10,718 14 2	
		Add Arrears to date (£539 19s. 9d.) Estimated to realise as per Balance Sheet	350 0 0	
350 0 0				
— — —		Subscriptions in suspense (£1825 14s. 6d.)	— — —	
	10,028 15 7			11,068 14 2
	511 17 10	„ Dividends on Investments		493 4 7
	465 19 2	„ Income Tax recovered		466 14 2
	— — —	„ Donations		60 0 0
	70 0 6	„ Miscellaneous Receipts		52 13 8
	£11,100 3 7			£12,186 6 7

1942 £ s. d.	1942 £ s. d.	*Expenditure.*	1943 £ s. d.	1943 £ s. d.
		By Administration Expenses:		
2963 7 3		Office Salaries and Wages	3364 2 1	
153 9 6		Superannuation	172 5 11	
341 18 5		House Expenses, etc.	312 4 8	
84 0 0		Accountants' Charges	84 0 0	
		Miscellaneous Printing, Stationery and Office		
531 10 11		Expenses	390 0 0	
212 2 0		Postages	142 6 5	
46 8 6		Miscellaneous	61 11 4	
4332 16 7			4526 10 5	
		Less Transfer to Publications and Library:	£ s. d.	
381 1 10		Journal	356 12 0	
161 15 3		Abstracts A I	147 13 0	
161 15 3		„ A II	147 13 0	
161 15 3		„ A III	147 13 0	
219 8 7		Library Account	238 2 3	
			1037 13 3	
	3247 0 5			3488 17 2
	215 15 7	„ Expenses on Account of Conjoint Chemical Office		167 15 5
	46 18 9	„ Expenses of Meetings		40 19 4
	5 5 0	„ Donation		5 5 0
	5624 0 7	„ Balance of Expenditure on Publications to Publications Fund		6452 13 9
		„ Contribution to Library Fund:		
536 10 6		For Fittings, Furniture, Books, Periodicals, and Binding	850 9 4	
48 14 11		For Air Raid Precautions	39 0 6	
275 2 6		For War Damage Insurance	197 15 4	
344 18 5		Proportion of Maintenance	346 8 4	
1205 6 4			1433 13 6	
6 4 5		*Add* Balance due to Library Account	— — —	
— — —		*Less* Balance from Library Account	230 6 0	
	1211 10 9			1203 7 6
	200 0 0	„ Transfer to Staff Pensions Fund		300 0 0
	99 1 5	„ Expenses of Local Representatives		124 15 5
	1 1 0	„ Legal Expenses		— — —
	216 3 5	„ Air Raid Precautions		136 19 11
	147 16 4	„ Travelling Expenses of Members of Council...		120 18 6
396 2 6		„ War Damage Insurance	332 4 5	
		Less Transfer to Publications and Library:	£ s. d.	
39 15 5		Journal	44 18 11	
18 4 9		Abstracts A I	20 11 11	
18 4 9		„ A II	20 11 11	
3 5 11		„ A III	3 15 2	
275 2 6		Library Account	197 15 4	
			287 13 3	
	41 9 2			44 11 2
	44 1 2	„ Balance, being Excess of Income over Expenditure, carried to Balance Sheet		100 3 5
	£11,100 3 7			£12,186 6 7

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1943.

PUBLICATIONS FUND.

1942 £ s. d.	1942 £ s. d.	*Income.*	1943 £ s. d.	1943 £ s. d.
		To Publication Sales (including back numbers):		
2309 17 6		Journals and Proceedings	2756 1 0	
9 7 10		Collective Index	76 10 9	
735 0 6		Annual Reports on Progress of Chemistry ...	594 13 3	
148 0 5		Authors' Extra Reprints	139 8 6	
2 11 3		Other Publications	6 4 9	
	3204 17 6			3572 18 3
		„ Net Proceeds of Advertisements:		
479 8 7		Journal	742 7 5	
110 6 1		Annual Reports	91 5 10	
	589 14 8			833 13 3
		„ Donations:		
22 12 0		Fellows	9 11 6	
1000 0 0		Chemical Council	1000 0 0	
50 0 0		„ for Summaries to Papers in Journal"	50 0 0	
	1072 12 0			1059 11 6
	300 0 0	„ Government Publications Grant (through the Royal Society		200 0 0
	400 0 0	„ Allocation from the Rockefeller Grant (through the Royal Society)		500 0 0
	37 16 0	„ Transfer from the Tilden Lecture Fund ...		12 12 0
	228 7 11	„ Dividends on Investments		202 8 9
	220 18 1	„ Income Tax recovered		232 2 8
	5624 0 7	„ Transfer from General Purposes Account (the balance of expenditure on publications) ...		6452 13 9
	£11,678 6 9			£13,066 0 2

1942 £ s. d.	1942 £ s. d.	*Expenditure.*	1943 £ s. d.	1943 £ s. d.
		By Expenses on account of Journal:		
1156 5 3		Editorial Salaries	1173 0 0	
85 12 6		Superannuation	85 12 6	
16 3 9		Editorial Postages	18 10 5	
2862 4 6		Printing and Paper	2884 0 3	
473 1 7		Banding and Distribution	510 9 10	
354 1 2		Authors' Reprints	342 10 9	
9 7 1		Miscellaneous	9 19 11	
381 1 10		Overhead Expenses (proportion)	356 12 0	
39 15 5		War Damage Insurance	44 18 11	
	5377 13 1			5425 14 7
		„ Contributions to Bureau:		
		Balance of Expenditure on Abstracts A I and A II	1977 7 5	
2221 19 9		Agreed amount to Abstracts A III	1500 0 0	
1500 0 0				
	3721 19 9			3477 7 5
	1250 0 0	„ Transfer to Special Reserve Fund		3000 0 0
	325 0 0	„ Transfer for Quinquennial Index, 1938–1942		300 0 0
	1003 13 11	„ Annual Reports on the Progress of Chemistry: Printing and Honoraria		862 18 2
	£11,678 6 9			£13,066 0 2

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1943.

LIBRARY.

1942 £ s. d.	1942 £ s. d.	*Income.*	1943 £ s. d.	1943 £ s. d.
		To Contribution for Fittings, Furniture, Books, Periodicals and Binding:		
536 10 6		Transfer from General Purposes Account ...	850 9 4	
		„ Air Raid Precautions:		
48 14 11		Transfer from General Purposes Account ...	39 0 6	
		„ War Damage Insurance:		
275 2 6		Transfer from General Purposes Account ...	197 15 4	
	860 7 11			1087 5 2
		„ Contributions towards maintenance:		
		Through the Chemical Council:		
		Chemical Society (transfer from General Purposes Account)	346 8 4	
344 18 5		Royal Institute of Chemistry	721 13 10	
718 11 8		Society of Chemical Industry	375 5 7	
373 13 3		From the Chemical Council	250 0 0	
250 0 0				
	1687 3 4			1693 7 9
		„ Contributions, etc., received from other sources towards maintenance):		
		Association of British Chemical Manufacturers	100 0 0	
100 0 0		Biochemical Society	21 0 0	
21 0 0		Faraday Society	26 5 0	
26 5 0		Institute of Brewing	50 0 0	
50 0 0		Society of Dyers and Colourists	10 10 0	
10 10 0		Society of Public Analysts	21 0 0	
21 0 0		Fellows	3 0 0	
4 1 0		Miscellaneous receipts	20 7 6	
9 8 4				
	242 4 4			252 2 6
	6 4 5	„ Balance, amount transfered from General Purposes Account		— — —
	£2796 0 0			£3032 15 5

1942 £ s. d.	1942 £ s. d.	*Expenditure.*	1943 £ s. d.	1943 £ s. d.
		By Capital and Extraordinary Expenditure:		
229 6 0		Books and Periodicals *	308 6 1	
7 4 6		Binding	42 3 3	
300 0 0		Transfer to Special Reserve Fund	500 0 0	
48 14 11		Air Raid Precautions	39 0 6	
275 2 6		War Damage Insurance	197 15 4	
	860 7 11			1087 5 2
		„ Maintenance:		
1484 14 5		Salaries	1334 0 0	
187 6 6		Superannuation of Library Staff	95 15 5	
27 19 8		Postages	33 0 0	
16 2 11		Miscellaneous Expenses	14 6 7	
219 8 7		Overhead Expenses (proportion)	238 2 3	
	1935 12 1			1715 4 3
	— — —	„ Balance, amount transferred to General Purposes Account		230 6 0
	£2796 0 0			£3032 15 5

* Other than those received in exchange.

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1943.

SPECIAL RESERVE FUND.

1942	Income.	1943	1942	Expenditure.	1943
£ s. d.		£ s. d.	£ s. d.		£ s. d.
54 8 2	To Dividends on Investments	120 3 7		By Balance, being Excess of Income over Expenditure, carried to Balance	
11 14 2	„ Interest on Deposit at Bankers and in Post Office Savings Bank	13 0 6	70 16 11	Sheet	192 13 6
4 14 7	„ Income Tax recovered	59 9 5			
£70 16 11		£192 13 6	£70 16 11		£192 13 6

RESEARCH FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
398 18 1	To Dividends on Investments	398 18 2	20 0 0	By Honorarium, Longstaff Medallist	— — —
365 4 11	„ Income Tax recovered	365 4 11	2 10 0	„ Longstaff Medal	— — —
2 16 1	„ Repayment of Grants	57 7 6	37 0 0	„ Grants	177 0 0
10 10 0	„ Grants not claimed	10 0 0	1 13 5	„ Miscellaneous Expenses	1 0 2
2 10 10	„ Interest on Deposit	1 14 6		„ Balance, being Excess of Income over Expenditure, carried to Balance	
20 0 0	„ Donation	— — —	738 16 6	Sheet	656 7 6
— — —	„ Sale of Chemicals	1 2 7			
£799 19 11		£834 7 8	£799 19 11		£834 7 8

SPECIAL PUBLICATIONS FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.
		To Sales of Publications:			By Balance, being Excess of Income over Expenditure, carried to Balance	
14 4 0		Memorial Lecture, Vol. I	8 16 0		Sheet	107 5 1
9 8 5		„ „ Vol. II	9 6 5	113 4 3		
6 3 6		„ „ Vol. III	5 5 3			
3 19 6		Faraday Lectures	2 15 8			
8 6		Portraits	— — —			
1 13 0		Other publications	2 15 11			
	35 16 11			28 19 3		
	74 0 8	„ Dividend on Investments		74 0 8		
	3 6 8	„ Interest on Deposit		4 5 2		
	£113 4 3			£107 5 1	£113 4 3	£107 5 1

QUINQUENNIAL INDEX FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
325 0 0	To Transfer from General Purposes Account	300 0 0	200 0 0	By Bureau of Chemical and Physiological Abstracts	150 0 0
75 0 0	„ Cash received from Bureau of Chemical and Physiological Abstracts	85 0 0		„ Balance, being Excess of Income over Expenditure, carried to Balance	
7	„ Interest on Deposit	— — —	200 0 7	Sheet	235 0 0
£400 0 7		£385 0 0	£400 0 7		£385 0 0

INCOME AND EXPENDITURE ACCOUNTS OF OTHER FUNDS FOR THE YEAR ENDED 31ST DECEMBER, 1943.

CENTENARY FUND.

1942	*Income.*	1943	1942	*Expenditure.*	1943
£ s. d.		£ s. d.	£ s. d.		£ s. d.
25 7 11	To Interest on Deposit in Post Office Savings Bank and London Savings Bank	26 0 0	25 7 11	By Balance, being Excess of Income over Expenditure, carried to Balance Sheet	26 0 0
£25 7 11		£26 0 0	£25 7 11		£26 0 0

STAFF PENSIONS FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
200 0 0	To Transfer from General Purposes Account	300 0 0	92 10 0	By Pensions paid during 1943	130 0 0
62 12 5	„ Dividends on Investments	66 6 7		„ Balance, being Excess of Income over Expenditure, carried to Balance	
23 18 6	„ Income Tax recovered	35 10 10	194 0 11	Sheet	271 17 5
£286 10 11		£401 17 5	£286 10 11		£401 17 5

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
27 5 2	To Dividends on Investments	27 5 2	150 0 0	By Harrison Prize	— — —
25 2 0	„ Income Tax recovered	25 2 0	8 8 0	„ Harrison Plaque	— — —
1 8	„ Interest on Deposit	2 4		„ Balance, being Excess of Income over Expenditure, carried to Balance	
	„ Balance, being Excess of Expenditure over Income, carried to Balance		— — —	Sheet	52 9 6
105 19 2	Sheet	— — —			
£158 8 0		£52 9 6	£158 8 0		£52 9 6

Income and Expenditure Accounts of other Funds for the Year ended 31st December, 1943.

SPECIAL LECTURES FUND.

1942	*Income.*	1943	1942	*Expenditure.*	1943
£ s. d.		£ s. d.	£ s. d.		£ s. d.
33 18 4	To Dividends on Investments	33 18 4	25 0 0	By Honorarium	25 0 0
11 11 2	„ Income Tax recovered	11 11 2	6 1 6	„ Lecture Expenses	— — —
8 5	„ Interest on Deposit	9 7		„ Balance, being excess of Income over Expenditure, carried to Balance	
			14 16 5	Sheet	20 19 1
£45 17 11		£45 19 1	£45 17 11		£45 19 1

THE FARADAY LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d
6 11 3	To Dividends on Investments	6 11 4			
6 11 2	„ Income Tax recovered	6 11 3	13 2 5	By Balance, being Excess of Income over Expenditure, carried to Balance Sheet	13 3 9
— — —	„ Interest on Deposit	1 2			
£13 2 5		£13 3 9	£13 2 5		£13 3 9

THE TILDEN LECTURE FUND.

£ s. d.		£ s. d.	£ s. d.		£ s. d.
42 9 7	To Dividends on Investments	43 2 6	47 5 0	By Honorarium	15 15 0
30 11 0	„ Income Tax recovered	30 11 0	10 19 2	„ Lecture Expenses	6 7 0
5 11	„ Interest on Deposit	4 2	37 16 0	„ Transfer to Publications Fund, for cost of publication of Lectures ...	12 12 0
	„ Balance, being Excess of Expenditure over Income, carried to Balance			„ Balance, being Excess of Income over Expenditure, carried to Balance	
22 15 8	Sheet	— — —	— — —	Sheet	39 3 8
£96 0 2		£73 17 8	£96 0 2		£73 17 8

THE CHEMICAL SOCIETY.—BALANCE SHEETS, 31st December, 1943.

GENERAL PURPOSES.

1942 £ s. d.		1942 £ s. d.	*Liabilities.*	1943 £ s. d.		1943 £ s. d.
		1,534 18 7	To Subscriptions received in advance ...			1,670 16 11
		4,119 10 9	„ Sundry Creditors (Printing and other Expenses)			4,341 12 11
		— — —	„ Amount due to Special Reserve Fund			3,000 0 0
		1,000 0 0	„ Loan, The Chemical Council			— — —
			„ Excess of Assets over Liabilities as per last Balance Sheet	21,270 4 0		
21,401 9 0			*Add* Life Composition Fees (£135) (two-thirds)	90 0 0		
47 1 0			*Add* Profit on realisation of investment	33 1 11		
— — —			*Add* Excess of Income over Expenditure for year	100 3 5		
44 1 2						
21,492 11 2				21,493 9 4		
222 7 2			*Deduct* Loss on realisation of investment	— — —		
		21,270 4 0				21,493 9 4
		£27,924 13 4				£30,505 19 2

1942 £ s. d.		1942 £ s. d.	*Assets.*	1943 £ s. d.		1943 £ s. d.
		24,715 7 0	By Investments as per Schedule (cost or value when acquired)			24,848 8 11
		2,231 14 3	„ Sundry Debtors			2,255 15 9
		350 0 0	„ Subscriptions in Arrear (£539 19*s.* 9*d.*). Estimated to realise			350 0 0
		— — —	„ Subscriptions in Suspense (£1,825 14*s.* 6*d.*)			— — —
		330 7 9	„ Stock of Paper (Journal and Abstracts)			308 0 9
		297 4 4	„ Cash in hand			2,743 15 9
		£27,924 13 4				£30,505 19 2

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1943.

PUBLICATIONS FUND.

1942			*Liabilities.*	1943					
£	s.	d.		£	s.	d.	£	s.	d.
10,363	3	10	To Excess of Assets over Liabilities as per last Balance Sheet	10,363	3	10			
			Deduct Loss on realisation of Investment	798	18	1			
							9,564	5	9
							£9,564	5	9

1942			*Assets.*	1943		
£	s.	d.		£	s.	d.
10,363	3	10	By Investments as per Schedule (cost or value when acquired)	9,564	5	9
£10,363	3	10		£9,564	5	9

SPECIAL RESERVE FUND.

1942			*Liabilities.*	1943					
£	s.	d.		£	s.	d.	£	s.	d.
2900	0	0	To Reserve for Publications as per last Balance Sheet	6400	0	0			
1250	0	0	*Add* Amount transferred from General Purposes Account	3000	0	0			
			Add Transfer from the Chemical Council:						
1500	0	0	£1500 3% Savings Bonds, 1955/65	—	—	—			
750	0	0	£750 2½% National War Bonds, 1949/51	—	—	—			
							9400	0	0
800	16	0	„ Reserve for Library Books and Binding as per last Balance Sheet	800	16	0			
300	0	0	*Add* Amount transferred from General Purposes Account	500	0	0			
							1300	16	0
1400	0	0	„ Reserve for Research Fund as per last Balance Sheet	2150	0	0			
750	0	0	*Add* Amount transferred from Research Fund	700	0	0			
							2850	0	0
							100	0	0
24	3	3	„ Excess of Income over Expenditure brought forward	95	0	2			
70	16	11	*Add* Excess of Income over Expenditure for year	192	13	6			
							287	13	8
							£13,938	9	8

1942			*Assets.*	1943		
£	s.	d.		£	s.	d.
7350	0	0	By Investments as per Schedule (cost or value when acquired)	9000	0	0
150	0	0	„ Sundry Debtors (General Purposes Account)	3000	0	0
1534	7	0	„ Cash at Bank	1414	5	0
511	9	2	„ Cash on Deposit in Post Office Savings Bank	524	4	8
£9545	16	2		£13,938	9	8

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1943.

RESEARCH FUND.

1942 £ s. d.	1942 £ s. d.	*Liabilities.*	1943 £ s. d.	1943 £ s. d.
	11 13 2	To Sundry Creditors		35 19 10
18,554 8 1		„ Excess of Assets over Liabilities as per last Balance Sheet	18,543 4 7	
738 16 6		*Add* Excess of Income over Expenditure for year	656 7 6	
19,293 4 7			19,199 12 1	
750 0 0		*Deduct* Amounts transferred to Special Reserve Fund	700 0 0	
	18,543 4 7			18,499 12 1
	£18,554 17 9			£18,535 11 11

1942 £ s. d.	1942 £ s. d.	*Assets.*	1943 £ s. d.	1943 £ s. d.
18,377 9 5		By Investments as per Schedule (cost or value when acquired)		18,377 9 5
177 8 4		„ Cash at Bank		158 2 6
	£18,554 17 9			£18,535 11 11

SPECIAL PUBLICATIONS FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.
	12 4	To Sundry Creditors		11 1
2374 11 9		„ Excess of Assets over Liabilities as per last Balance Sheet	2487 16 0	
113 4 3		*Add* Excess of Income over Expenditure for year	107 5 1	
	2487 16 0			2595 1 1
	£2488 8 4			£2595 12 2

£ s. d.	£ s. d.		£ s. d.	£ s. d.
1600 0 0		By Investment as per Schedule (cost or value when acquired)		1600 0 0
1 2 10		„ Sundry Debtors		— — —
887 5 6		„ Cash at Bank		995 12 2
	£2488 8 4			£2595 12 2

QUINQUENNIAL INDEX FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.
		To Excess of Assets over Liabilities as per last Balance Sheet	250 0 7	
50 0 0		*Add* Excess of Income over Expenditure for year	235 0 0	
200 0 7				485 0 7
	250 0 7			
	£250 0 7			£485 0 7

£ s. d.	£ s. d.		£ s. d.	£ s. d.
250 0 0		By Sundry Debtors...		85 0 0
7		„ Cash at Bank		400 0 7
	£250 0 7			£485 0 7

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1943.

CENTENARY FUND.

1942 £ s. d.	1942 £ s. d.	*Liabilities.*	1943 £ s. d.	1943 £ s. d.	1942 £ s. d.	1942 £ s. d.	*Assets.*	1943 £ s. d.	1943 £ s. d.
1026 13 9		To Excess of Assets over Liabilities as per last Balance Sheet	1052 1 8		10 15 6		By Cash at Bank	10 15 6	
25 7 11		*Add* Excess of Income over Expenditure for year	26 0 0		1041 6 2		„ Cash on Deposit in Post Office Savings Bank and London Savings Bank	1067 6 2	
	1052 1 8			1078 1 8					
	£1052 1 8			£1078 1 8	£1052 1 8				£1078 1 8

STAFF PENSIONS FUND.

£ s. d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.
	12 10 0	To Sundry Creditors		12 10 0	3172 13 9		By Investments as per Schedule (cost or value when acquired)	3322 13 9	
3174 11 9		„ Excess of Assets over Liabilities as per last Balance Sheet	3368 12 8		208 8 11		„ Cash at Bank	330 6 4	
194 0 11		*Add* Excess of Income over Expenditure for year	271 17 5						
	3368 12 8			3640 10 1					
	£3381 2 8			£3653 0 1	£3381 2 8				£3653 0 1

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£ d.	£ s. d.		£ s. d.	£ s. d.	£ s. d.	£ s. d.		£ s. d.	£ s. d.
	8 8 0	To Sundry Creditors		— — —	1101 7 11		By Investments as per Schedule (cost or value when acquired)	1101 7 11	
1262 8 8		„ Excess of Assets over Liabilities as per last Balance Sheet	1156 9 6		63 9 7		„ Cash at Bank	107 11 1	
— — —		*Add* Excess of Income over Expenditure for year	52 9 6						
105 19 2		*Deduct* Excess of Expenditure over Income for year	— — —						
	1156 9 6			1208 19 0					
	£1164 17 6			£1208 19 0	£1164 17 6				£1208 19 0

THE CHEMICAL SOCIETY. BALANCE SHEETS, 31ST DECEMBER, 1943.

SPECIAL LECTURES FUND.

1942			*Liabilities.*	1943			1942			*Assets.*	1943		
£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
1154	2	1	To Excess of Assets over Liabilities as per last Balance Sheet	1168	18	6	1000	0	0	By Investment as per Schedule (cost or value when acquired)	1000	0	0
							168	18	6	„ Cash at Bank	189	17	7
14	16	5	*Add* Excess of Income over Expenditure for year	20	19	1							
			1168 18 6										
			£1168 18 6				£1168	18	6		£1189	17	7

THE FARADAY LECTURE FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
405	8	7	To Excess of Assets over Liabilities as per last Balance Sheet	418	11	0	369	4	0	By Investment as per Schedule (cost or value when acquired)	369	4	0
							49	7	0	„ Cash at Bank	62	10	9
13	2	5	*Add* Excess of Income over Expenditure for year	13	3	9							
			418 11 0										
			£418 11 0				£418	11	0		£431	14	9

THE TILDEN LECTURE FUND.

£	s.	d.		£	s.	d.	£	s.	d.		£	s.	d.
			25 4 0										
			To Sundry Creditors				12	12	0				
1962	14	9	„ Excess of Assets over Liabilities as per last Balance Sheet	1939	19	1	1878	14	10	By Investments as per Schedule (cost or value when acquired)	1878	14	10
							86	8	3	„ Cash at Bank	112	19	11
—	—	—	*Add* Excess of Income over Expenditure for year	39	3	8							
22	15	8	*Deduct* Excess of Expenditure over Income for year	—	—	—							
			1939 19 1										
			£1965 3 1				£1965	3	1		£1991	14	9

SCHEDULE OF INVESTMENTS.

GENERAL PURPOSES.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1943.* £ s. d.
£3629 6s. 9d. 5% Conversion Stock, 1944/64	3491 2 8	3706 9 3
£11,426 15s. 0d. 3½% Conversion Stock, 1961, or after	8874 2 2	11,969 10 5
£600 4% Funding Stock, 1960/90	480 0 0	679 10 0
£408 2s. 6d. 3% Funding Stock, 1959/69	394 11 5	411 3 9
£100 3% Savings Bonds, 1955/65	100 0 0	101 0 0
£1200 14s. 9d. 3% Savings Bonds, 1960/70	1200 14 9	1203 14 10
£1520 14s. 3d. Cardiff Corporation 3% Stock, 1914/54	1650 0 0	1520 14 3
£2400 Bristol Corporation 2½% Debenture Stock, 1957	2070 2 0	2280 0 0
£1200 Leeds Corporation 3% Stock	1143 1 0	1116 0 0
£787 London, Midland and Scottish Railway 4% Debenture Stock	839 3 7	822 8 4
£2713 London, Midland and Scottish Railway 4% Preference Stock	3572 0 4	2089 0 2
£1200 London and North Eastern Railway 3% Debenture Stock ...	1033 11 0	978 0 0
	£24,848 8 11	£26,877 11 0

PUBLICATIONS FUND.

£5260 19s. 9d. 3½% Conversion Stock, 1961, or after	3645 12 8	5510 17 11
£3173 1s. 6d. 5% Conversion Stock, 1944/64	3199 18 7	3240 10 1
£1000 3% Savings Bonds, 1955/65	1000 0 0	1010 0 0
£1261 1s. 11d. 3% Savings Bonds, 1960/70	1261 1 11	1264 5 1
£603 London, Midland and Scottish Railway 4% Guaranteed Stock	457 12 7	609 0 7
	£9564 5 9	£11,634 13 8

RESEARCH FUND.

£4498 11s. 0d. 5% Conversion Stock, 1944/64	4267 4 10	4594 2 10
£10,177 16s. 1d. 3½% Conversion Stock, 1961, or after	8833 2 3	10,661 5 0
£806 Victoria 3% Stock, 1929/49	706 6 2	797 18 10
£1000 London and North Eastern Railway 4% 2nd Guaranteed Stock	1010 0 0	900 0 0
£1034 Great Western Railway 2½% Debentures	1049 15 11	749 13 0
£1483 London, Midland and Scottish Railway 4% Debenture Stock	1508 3 6	1549 14 8
£1122 Metropolitan Water Board 3% "B" Stock	1002 16 9	1077 2 5
	£18,377 9 5	£20,329 16 9

SPECIAL RESERVE FUND.

£1000 3% National Defence Bonds	1000 0 0	1000 0 0
£2447 7s. 10d. 2½% National War Bonds, 1946/48	2450 0 0	2496 6 9
£1612 10s. 2d. 2½% National War Bonds, 1945/47	1650 0 0	1644 15 2
£2400 2½% National War Bonds, 1949/51	2400 0 0	2403 0 0
£1500 3% Savings Bonds, 1955/65	1500 0 0	1515 0 0
	£9000 0 0	£9059 1 11

SPECIAL PUBLICATIONS FUND.

Nominal Details.	*Cost or Value when Acquired.* £ s. d.	*Market Value 31st December, 1943.* £ s. d.
£2115 8s. 10d. 3½% Conversion Stock, 1961, or after	£1600 0 0	£2215 18 6

STAFF PENSIONS FUND.

£683 6s. 1d. 3½% Conversion Stock, 1961, or after	527 13 9	715 15 2
£371 17s. 1d. 5% Conversion Stock, 1944/64	375 0 0	379 15 1
£2100 2½% National War Bonds, 1946/48	2100 0 0	2142 0 0
£150 2½% National War Bonds, 1951/53	150 0 0	150 15 0
£170 3% Savings Bonds, 1955/65	170 0 0	171 14 0
	£3322 13 9	£3559 19 3

THE EDWARD FRANK HARRISON MEMORIAL TRUST FUND.

£61 15s. 8d. 3½% Conversion Stock, 1961, or after	50 1 5	64 14 3
£1255 London, Midland and Scottish Railway 4% Debenture Stock	1051 6 6	1311 9 6
	£1101 7 11	£1376 3 9

SPECIAL LECTURES FUND.

£1299 9s. 4d. 3½% Conversion Stock,, 1961 or after	£1000 0 0	£1361 3 10

THE FARADAY LECTURE FUND.

£374 19s. 0d. 3½% Conversion Stock, 1961, or after	£369 4 0	£392 15 2

THE TILDEN LECTURE FUND.

£419 4s. 10d. 3% Funding Stock, 1959/69	386 12 10	422 7 8
186 National Provincial Bank Shares £5 each, £1 paid "B"	678 18 0	697 10 0
£532 London Transport "B" 5% Stock	625 2 0	630 8 5
£220 Metropolitan Water Board (Kent Water Works) 3% Deb. Stock	188 2 0	203 10 0
	£1878 14 10	£1953 16 1

F. P. DUNN, *Treasurer.*

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers of the Society, and certify them to be in accordance therewith. We have also verified the Balances at the Bankers and the Investments.

224, REGENT STREET, W. 1.
24th March, 1944.

W. B. KEEN & CO.,
Chartered Accountants.

APPENDIX A.

REPORT OF THE BUREAU OF CHEMICAL AND PHYSIOLOGICAL ABSTRACTS FOR THE YEAR 1943.

In March, 1943, the British Commonwealth Science Committee, under the Chairmanship of the President of the Royal Society, issued a report in which attention was drawn to the need for a rationalisation of effort in the provision of an efficient and widespread information service. The report refers, *inter alia*, to the major abstracting services in this country, including the Imperial Agricultural Bureaux, the Bureau of Hygiene and Tropical Medicine, Science Abstracts, and the Bureau of Chemical and Physiological Abstracts, and stresses the overlap particularly between the scope of the last two. The Bureau, well aware of the overlap, not only with the major abstracting organisations, but with Societies issuing abstracts of more specialised character, has sought, by negotiation, to reduce this duplication of effort.

The policy of the Bureau has been to cover as completely as possible the fields of science with which it deals by means of "indicative abstracts." War-time limitations of paper have handicapped the Editor and Abstractors, but it has been the length of the abstract and not the number of abstracts which has been decreased. The Bureau does not assume the right to judge the value of any paper or article: it considers it to be its duty to reflect dispassionately all the published scientific work which comes within its field.

In November, 1943, the Bureau celebrated the 20th Anniversary of its formation, and offered its congratulations and thanks to Mr. Julian Baker, who, as a representative of the Society of Chemical Industry, is the only member who has served continuously for the whole twenty years. The thanks of the Bureau were also accorded to Dr. C. R. Harington, who resigned his membership as a representative of the Chemical Society at the end of the year. It is difficult to speak too highly of the help given by Dr. Harington during his five years' membership of the Bureau.

As indicated above, the Officers of the Bureau have continued to discuss with representatives of other bodies, including the Management Committee of Science Abstracts, the possibilities of collaboration with the Bureau, but these discussions have not so far led to definite results, except in the case of the Society for Experimental Biology. Arrangements have now been made whereby that Society is to become a supporting Society of the Bureau on the basis of an annual contribution and a reduced price of Abstracts A III to its members. The Bureau is glad to have this opportunity of welcoming the latest participating Society and of expressing its appreciation of the offer of assistance in sub-editing certain sections of the Abstracts A III, which has been gratefully accepted.

The Bureau, with the concurrence of the Chemical Society, the Society of Chemical Industry, and the Physiological Society, has agreed to a request of the Biochemical Society to appoint a representative on the Bureau. The Bureau was glad to be able to accede to this request of the Biochemical Society in view of the continued interest which that Society has evinced during so many years in the work of the Bureau. Professor F. G. Young has become a member of the Bureau as nominee of the Biochemical Society.

Although the Bureau is responsible for the preparation and publication of all its abstracts and is, in fact, the publisher of its Annual and Collective Indexes, hitherto the Chemical Society has been officially the publisher of Abstracts A, and the Society of Chemical Industry of Abstracts B. This anomaly has now been removed, for with the consent of the Chemical Society and the Society of Chemical Industry the Bureau has been authorised to act as Publisher of all its abstracts and indexes.

The proceeds of sales of the Collective Indexes of Abstracts during the year were:

	£	s.	d.
Decennial Index	57	0	0
Quinquennial Index, 1932—37	219	0	0

Another matter which has been under review is the liability of members of the Bureau in respect of contracts entered into by the Bureau. Under present circumstances members of the Bureau have an unlimited personal liability, since the Bureau is an unincorporated body. Acting on legal advice, and with the approval of the supporting Societies, it has been decided to take the necessary steps to incorporate the Bureau by the formation of a Company under the Companies Act, limited by guarantee and not having a share capital.

Consideration has been given to criticisms of the Indexes of the Abstracts, and a Sub-Committee has been appointed to consider possible improvements.

Early in the year a Sub-Committee was appointed to consider the classification and sub-division of the Abstracts as a whole. This Committee in due course presented a comprehensive report dealing with all the sections of the Abstracts excepting A II, the classification of which has only recently been

rearranged. Acting on this report the Bureau made a number of minor alterations in the titles of various sections of the Abstracts, but the most important result of the recommendations of the Sub-Committee was the decision to issue a separate section of the Abstracts containing all matter relating to analysis and laboratory apparatus; it was further recommended that the distribution of the Abstracts on vitamins between the various sections should receive further consideration. The valuable work of this Sub-Committee led to the appointment of a further special Sub-Committee to consider these last two recommendations.

The Sub-Committee on analysis consisted of members of the Bureau together with Dr. A. Parker and two representatives of the Society of Public Analysts. After a number of detailed discussions the Bureau agreed, on the reports of the Sub-Committee, that the new section of the Abstracts should be called "C Analysis and Apparatus" and classified as follows: I, Inorganic, pure and applied; II, Organic, pure and applied; III, Physiology, Biochemistry, Foods, Sanitation, Agriculture; IV, General technique and laboratory apparatus.

Sections A and B of the Abstracts will therefore in future contain no abstracts dealing with analytical methods and laboratory apparatus (chemical plant will, as before, be dealt with in B I), but cross-references to abstracts in section C will be inserted in appropriate places in A and B. There are many papers in which descriptions of analytical methods or apparatus are only a part; such papers will be represented by two abstracts, one in section C giving the matter relevant to that section and the other in its usual place in A or B dealing with the remainder of the investigation. Dr. E. B. Hughes will act as Assistant Editor of section C, and a "C Abstracts Sub-Committee" has been appointed consisting of the Honorary Officers of the Bureau, Dr. Hughes, Mr. R. C. Chirnside, Mr. B. S. Cooper, Dr. E. J. King, Dr. A. Parker, and the Secretary of the Bureau. It was further decided that this section of the Abstracts should be available without extra charge to all members who already receive one or more sections of the Abstracts, and that the price to non-members should be 15*s.* per annum, including the separate index.

The recommendation, mentioned above, regarding abstracts on vitamins was also referred to a special Sub-Committee consisting of members of the Bureau and representatives of the Nutrition Society and of the Food Group of the Society of Chemical Industry. On the report of this Sub-Committee, it was decided that all abstracts relating to vitamins other than those which are mainly technological or analytical should be placed in A III section xviii, and that the title of this section should be changed to "Animal Nutrition" with five sub-headings: General; Carbohydrates and Fats; Proteins and Amino-Acids; Minerals and Trace Elements; and Vitamins; and that a reference to the section of metabolism should be inserted at the end of section xviii. In view of the paucity of abstracts dealing with nutrition subjects other than vitamins the insertion of the first four of the above sub-headings has been postponed, so that the class has now only one sub-heading "Vitamins."

In the last Annual Report it was mentioned that for the first time a comprehensive picture of the cost to the chemical community of the abstracting service was possible. In a similar way the Annual Income and Expenditure Accounts for 1943 (see Appendix I) can be summarised as follows (figures for 1942 are included for comparison):

EXPENDITURE.

1942. £		1943. £
	Cost of production:	
2159	A I	2010
2479	A II	2245
3845	A III	3928
2371	B I	2493
2084	B II	2087
1464	B III	1690
£14,102		£14,453

INCOME.

1942. £	£		1943. £	£
		Sales and advertisements:		
2091		A I and A II	2217	
2004		A III	2195	
1877		B I, B II, B III	2733	
—	5972		—	7145
		Contributions:		
3722		Chemical Society	3477	
4068		Society of Chemical Industry	3609	
100		Institute of Chemistry	—	
400		Physiological Society	400	
300		Biochemical Society	300	
100		Anatomical Society	100	
312		Chemical Council	380	
—		Miscellaneous	97	
—	9002		—	8363
	£14,974			£15,508
	872	*Less* placed to reserve and balance		1055
	£14,102			£14,453

Cost of production has therefore risen by some £350 while sales and advertisements have increased by nearly £1200, a most encouraging feature, reflecting as it does the desire of persons outside the Societies contributing to the scheme to obtain the publications of the Bureau.

It is to be remembered that the Chemical Society and the Society of Chemical Industry respectively meet the balance of expenditure on A I and A II and on B I, B II, and B III, and the increased sales of these sections means that whereas the Chemical Society contributed some £2220 last year, it has only been called upon to provide £1980 this year. Similarly the Society of Chemical Industry contributed £3823 last year and £3534 this year. The contribution of the two Societies to the A III Fund remains as last year, namely £1500 by the Chemical Society and £75 by the Society of Chemical Industry; a gift of £380 from the Chemical Council in respect of Abstracts A III is also gratefully acknowledged.

The figures in Appendix II show that the total number of abstracts printed in 1943 was 25,195 (1436 pages) compared with 26,008 (1534 pages) in 1942, a decrease of 813 in number of abstracts and 98 in pages. That these decreases are so small, despite the reduced size of many of the publications still available, is largely due to the fact that the Bureau has been able to borrow a number of German journals from the Libraries of the National Physical Laboratory, the Chemical Research Laboratory, and certain branches of Imperial Chemical Industries, as well as from the Science Library. The Bureau welcomes this opportunity of expressing its cordial appreciation of these facilities.

Finally, the Bureau wishes to place on record its grateful thanks to the Assistant Editors and Abstractors, who have continued to devote much of their very limited spare time to the preparation of the abstracts.

Appendix II.

The figures given in the appended tables show the number of abstracts and pages printed in each section during 1943, together with comparative figures for 1942.

	A I.				A II.				A III.			
	1942.		1943.		1942.		1943.		1942.		1943.	
Quarter.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.
1st	742	62	741	38	414	62	307	38	2339	140	2106	110
2nd	845	48	994	48	341	44	482	52	2052	112	2224	114
3rd	899	44	671	36	371	40	447	54	2328	110	2571	128
4th	1108	52	743	40	611	70	403	58	2394	114	2091	112
	3594	206	3149	162	1737	216	1639	202	9013	476	8992	464

	B I.				B II.				B III.			
	1942.		1943.		1942.		1943.		1942.		1943.	
Quarter.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.	No. of Abs.	Pages.
1st	1466	88	1279	66	921	68	897	50	779	48	652	34
2nd	1055	52	1421	64	897	56	902	52	590	32	571	36
3rd	1258	56	1294	62	958	52	885	50	454	24	734	44
4th	1564	74	1260	62	926	50	836	48	796	36	684	40
	5343	270	5254	254	2702	226	3520	200	2619	140	2641	154

Appendix I.

BUREAU OF CHEMICAL AND PHYSIOLOGICAL ABSTRACTS.

INCOME AND EXPENDITURE ACCOUNT OF ABSTRACTS A I AND A II FOR THE YEAR ENDED 31ST DECEMBER, 1943.

1942	*Expenditure.*		1943		
£ s. d.		£ s. d.	£ s. d.	£ s. d.	
	Abstracts A I:				
405 6 0	To Editorial Salaries	383 16 0			
24 10 5	„ Postages	22 9 9			
293 5 9	„ Abstractors' Fees	242 10 3			
762 2 2	„ Printing and Paper	678 4 8			
117 7 5	„ Banding and Distribution ...	145 11 11			
45 5 1	„ Miscellaneous (including War Damage Insurance)	49 5 9			
1647 16 10			1521 18 4		
	„ Index—				
68 2 0	Salaries	64 0 8			
4 18 5	Superannuation	4 12 1			
175 1 7	Printing and Paper	181 13 9			
18 0 9	Banding and Distribution ...	20 4 2			
30 9 1	Miscellaneous	3 7 4			
296 11 10			273 18 0		
161 15 3	„ Share of Overhead Expenses, The Chemical Society	147 13 0			
53 0 0	„ Share of Overhead Expenses, Society of Chemical Industry	65 6 8			
214 15 3			212 19 8		
2159 3 11				2008 16 0	
	Abstracts A II:				
311 3 5	To Editorial Salaries	316 16 8			
24 7 11	„ Postages	22 7 3			
309 19 2	„ Abstractors' Fees	302 7 10			
875 0 1	„ Printing and Paper	913 7 4			
117 7 5	„ Banding and Distribution ...	145 11 11			
45 5 1	„ Miscellaneous (including War Damage Insurance)	49 5 8			
1683 3 1			1750 16 8		
	„ Index—				
71 19 3	Salaries	79 17 0			
4 18 5	Superannuation	4 12 1			
156 0 7	Printing and Paper	172 2 0			
18 0 9	Banding and Distribution ...	21 17 0			
30 2 2	Miscellaneous	4 3 11			
281 1 2			282 12 0		
161 15 3	„ Share of Overhead Expenses, The Chemical Society	147 13 0			
53 0 0	„ Share of Overhead Expenses, Society of Chemical Industry	65 6 8			
214 15 3			212 19 8		
2178 19 6				2246 8 4	
£4338 3 5				£4255 4 4	

1942	*Income.*	1943	
£ s. d.		£ s. d.	
2070 0 8	By Sales of Abstracts A I and A II	2217 4 11	
21 3 0	„ Net Revenue from Advertisements	60 12 0	
25 0 0	„ Contribution, The Royal Institute of Chemistry	— — —	
2221 19 9	„ Transfer from The Chemical Society Publications Fund (the balance of Expenditure on Abstracts A I and A II)	1977 7 5	
£4338 3 5		£4255 4 4	

Income and Expenditure Account of Abstracts A III for the Year ended 31st December, 1943.

1942 £ s. d.	1942 £ s. d.	*Expenditure.*	1943 £ s. d.	1943 £ s. d.
531 7 10		To Editorial Salaries	557 4 6	
30 8 11		„ Postages	27 6 5	
691 1 11		„ Abstractors' Fees	699 14 10	
1508 14 7		„ Printing and Paper	1563 9 0	
117 7 4		„ Banding and Distribution	145 1 2	
20 18 1		„ Miscellaneous (including War Damage Insurance)	30 12 10	
	2899 18 8			3023 8 9
		„ Index:		
156 14 10		Editorial Salaries	183 8 2	
11 2 0		Superannuation	11 14 8	
465 5 2		Printing and Paper	465 15 9	
23 10 0		Banding and Distribution	21 1 11	
73 2 10		Miscellaneous	9 12 9	
	729 14 10			691 13 3
161 15 3		„ Share of Overhead Expenses, Chemical Society	147 13 0	
53 0 0		„ Share of Overhead Expenses, Society of Chemical Industry	65 6 8	
	214 15 3			212 19 8
	700 0 0	„ Transfer to Reserve Fund		950 0 0
	171 10 5	„ Excess of Income over Expenditure, carried to Balance Sheet		105 2 6
	£4715 19 2			£4983 4 2

1942 £ s. d.	1942 £ s. d.	*Income.*	1943 £ s. d.	1943 £ s. d.
	1989 12 1	By Sales of Abstracts A III		2195 3 5
	11 7	„ Sales of Physiological Abstracts		— — —
		„ Contributions:		
1500 0 0		The Chemical Society (Annual Grant)	1500 0 0	
400 0 0		The Physiological Society	400 0 0	
300 0 0		The Biochemical Society	300 0 0	
100 0 0		The Anatomical Society	100 0 0	
75 0 0		The Society of Chemical Industry	75 0 0	
312 0 0		The Chemical Council	380 0 0	
25 0 0		The Royal Institute of Chemistry	— — —	
	2712 0 0			2755 0 0
	3 4 0	„ Interest on Deposit		2 14 9
	10 11 6	„ Net Revenue from Advertisements		30 6 0
	£4715 19 2			£4983 4 2

Balance Sheet of Abstracts A III for the Year ended 31st December, 1943.

Liabilities. £ s. d.	£ s. d.	1943 £ s. d.	*Assets.* £ s. d.	£ s. d.	1943 £ s. d.
1082 15 8	To Sundry Creditors	1469 0 2	800 3 7	By Sundry Debtors	1225 4 4
— — —	„ Amount due to Reserve Fund	950 0 0	454 16 0	„ Cash at Bank	1471 2 3
13 6	„ Excess of Assets over Liabilities as per last Balance Sheet	172 3 11			
171 10 5	*Add* Excess of Income over Expenditure for year	105 2 6			
172 3 11		277 6 5			
£1254 19 7		£2696 6 7	£1254 19 7		£2696 6 7

Income and Expenditure Account of Abstracts A III Reserve Fund for the Year ended 31st December, 1943.

1942	*Expenditure.*	1943	1942	*Income.*	1943
£ s. d.		£ s. d.	£ s. d.		£ s. d.
£5 3 0	To Excess of Income over Expenditure carried to Balance Sheet	£28 11 6	£5 3 0	By Dividend on Investments	£28 11 6

Balance Sheet of Abstracts A III Reserve Fund for the Year ended 31st December, 1943.

Liabilities.						*Assets.*			
£ s. d.	£ s. d.		£ s. d.	£ s. d.		£ s. d.		£ s. d.	
700 0 0		To Excess of Assets over Liabilities as per last Balance Sheet	1405 3 0			1400 0 0	By Investments as per Schedule (cost or value when acquired)	1400 0 0	
		Add Amount transferred from Abstract A III Account	950 0 0			— — —	„ Sundry Debtors	12 0 11	
700 0 0						— — —	„ Amount due from A III Account	950 0 0	
		Add Excess of Income over Expenditure for year	28 11 6			5 3 0	„ Cash at Bank	21 13 7	
5 3 0									
	1405 3 0			2383 14 6					
	£1405 3 0			£2383 14 6		£1405 3 0		£2383 14 6	

F. P. Dunn,
Treasurer of Bureau.

We have examined the above Balance Sheets and accompanying Income and Expenditure Accounts with the Books and Vouchers, and certify them to be in accordance therewith. We have also verified the Balances at the Bankers and the Investments.

224, Regent Street, W. 1.
24th March, 1944.

W. B. Keen & Co.,
Chartered Accountants.

Schedule of Investments of Abstracts A III Reserve Fund.

	Value or Cost when Acquired.	Market Value 31st December, 1943.
	£ s. d.	£ s. d.
£700 3% Savings Bonds, 1955/65	700 0 0	707 0 0
£700 2½% National War Bonds, 1951/53	700 0 0	703 10 0
	£1400 0 0	£1410 10 0

BUREAU OF CHEMICAL AND PHYSIOLOGICAL ABSTRACTS.

INCOME AND EXPENDITURE ACCOUNT OF ABSTRACTS B I, B II AND B III FOR THE YEAR ENDING 31ST DECEMBER, 1943.

1942 £ s. d.	1942 £ s. d.	*Expenditure.*	1943 £ s. d.	1943 £ s. d.
		Abstracts B I:		
407 9 5		To Editorial Salaries	438 3 3	
16 1 5		„ Postages	17 17 4	
390 6 6		„ Abstractors' Fees	353 4 2	
933 19 6		„ Printing and Paper	992 19 3	
114 18 2		„ Binding and Distribution	129 6 10	
22 8 6		„ Miscellaneous	19 11 11	
	1885 3 6			1980 2 9
		„ Index—		
92 9 5		Salaries	100 8 0	
235 6 4		Printing and Paper	253 18 2	
21 2 5		Binding and Distribution ...	29 6 2	
30 15 8		Miscellaneous	5 5 7	
	379 13 10			387 18 11
	106 6 8	„ Share of Overhead Expenses ...		125 6 8
	2371 4 0			2493 6 4
		Abstracts B II:		
341 1 0		To Editorial Salaries	345 0 1	
16 1 5		„ Postages	17 17 4	
325 19 3		„ Abstractors' Fees	300 19 0	
847 19 10		„ Printing and Paper	843 16 10	
114 18 0		„ Binding and Distribution	129 6 10	
22 8 6		„ Miscellaneous	19 11 11	
	1668 8 0			1656 12 0
		„ Index—		
77 6 0		Salaries	79 1 2	
189 5 11		Printing and Paper	199 1 2	
16 18 5		Binding and Distribution ...	23 0 5	
25 15 3		Miscellaneous	4 3 1	
	309 5 7			305 5 10
	106 6 8	„ Share of Overhead Expenses ...		125 6 8
	2084 0 3			2087 4 6
		Abstracts B III:		
211 7 7		To Editorial Salaries	265 13 1	
16 1 5		„ Postages	17 17 3	
199 6 11		„ Abstractors' Fees	231 14 8	
567 16 0		„ Printing and Paper	664 16 11	
114 18 0		„ Binding and Distribution	129 6 10	
22 8 6		„ Miscellaneous	19 11 11	
	1131 18 5			1329 0 8
		„ Index—		
47 19 3		Salaries	60 17 5	
148 17 10		Printing and Paper	163 1 5	
13 4 7		Binding and Distribution ...	17 14 0	
15 19 4		Miscellaneous	3 4 0	
	226 1 0			234 16 10
	106 6 8	„ Share of Overhead Expenses ...		125 6 8
	1464 6 1			1689 4 2
	£6919 10 4			£6369 15 0

1942 £ s. d.	*Income.*	1943 £ s. d.	1943 £ s. d.
1873 19 9	By Sales of Abstracts	2732 16 9	
2 13 5	„ Share of Fees and Sundry Sales	2 2 5	
1876 13 2			2735 19 2
60 0 0	„ The Royal Institute of Chemistry Grant ...		
3992 17 2	„ Excess of Expenditure over Income transferred to Society of Chemical Industry ...		3533 15 10
£6919 10 4			£6369 15 0

APPENDIX B.

ANNUAL REPORT OF THE JOINT LIBRARY COMMITTEE, 1943.

The Library has been more intensively used during 1943 than in any previous year. Attendances show an increase of 1,272 over those recorded in 1942, the number of books borrowed increased by 966, and 289 more volumes were issued by post than in the previous year.

Telephone enquiries increased by 318, the total for 1943 numbering 1,417.

The most marked increase was in photostat copying, the number of printed pages copied (2,873) not only being an increase of 1,113 over the 1942 figures, but also 789 more than in the year 1926, which had been the record year for photostat copying.

138 books were added to the Library, of which 34 were presented. These, together with 334 volumes of periodicals, give a total for the year of 472 volumes added. There are now 45,599 volumes in the Library, consisting of 13,590 books and 32,009 volumes of periodicals.

	Attendances.	Books borrowed.	Books added.	Volumes of periodicals.	Pamphlets.
1943	6692	6824 (2831 by post)	138	334	236
1942	5420	5858 (2542 by post)	195	302	208

The Microfilm Reader has been considerably used by readers to consult the microfilm copies of the *Berichte* and *Liebig's Annalen* for 1940 to 1943. Arrangements have been made by which it is hoped to obtain many of the German chemical periodicals published since 1939.

The direct importation of books from the United States has resulted in their being available in the Library with much less delay than previously.

The Committee desires to express its sincere thanks to Fellows and others who have so kindly presented books to the Library, and also to Professor E. L. Kennaway, F.R.S., for his welcome gift of a bronze medal issued to celebrate the 60th year of Albrecht Kossel.

Attention must again be called to gravely inadequate accommodation. In the past it has been the growth of the Library which has caused the greatest concern. Temporary relief has been gained by placing shelving in odd corners and sending books away to storage. Such extra shelving has been at the expense of room for readers, and the space gained by storing books has been filled with later additions, so that when these books are required at the end of the war there will be no room for them.

The development now recorded, of intensive and ever-increasing use of the Library, cannot be met by any such expedient. The present accommodation is taxed to the utmost—indeed, frequently over-taxed—and the only possibility in the present building would appear to be to use the present meeting room for further shelving and as a reading-room, and for meetings to be held elsewhere. Even this would only be a makeshift, and it is difficult to see how the rapidly increasing demands on the services of the Library can be met until it is housed in premises more befitting its national importance.

APPENDIX C.

LECTURES, ETC.

In London.

31st January, *meeting* for reading papers; 18th February, *Tilden Lecture*, "Aspects of Nucleotide Chemistry," by Professor J. M. Gulland; 26th March, *Presidential Address*, "Stereochemistry of Labile Compounds," by Dr. W. H. Mills; 15th April, *Liversidge Lecture*, "Magnetochemistry," by Professor S. Sugden; 21st October, *meeting* for reading papers; 18th November, *Lecture*, "Wave Mechanics and Colour of Organic Compounds," by Mr. E. J. Bowen.

Outside London.

Cambridge. 13th May, in the Lecture Room of the Chemical Laboratories, Pembroke Street, *official meeting* for reading papers.

Edinburgh. 18th February, at the North British Station Hotel (joint meeting with the Local Sections of the R.I.C. and S.C.I.), *lecture*, "The Chemistry of Hashish," by Professor A. R. Todd; 16th November, in the Lecture Theatre of the University, *lecture*, "The Strength of Carbon Bonds," by Professor M. Polanyi.

Glasgow. 19th February, at the Royal Technical College (joint meeting with the Local Sections of the R.I.C. and the S.C.I.), *lecture*, "The Chemistry of Hashish," by Professor A. R. Todd; 10th November, in the Chemistry Lecture Theatre (joint meeting with the Glasgow University Alchemists Club and the Andersonian Chemical Society), *lecture*, "Humour and Humanism in Chemistry," by Professor John

Read; 3rd December, at the Royal Technical College (joint meeting with the Local Sections of the R.I.C. and the S.C.I.), *lecture*, " Some Aspects of the Formation of Ring Compounds," by Professor G. M. Bennett.

Leeds. 9th March (joint meeting with the University of Leeds Chemical Society), exhibition of scientific films and apparatus, and *lecture*, " The Synthesis of High Polymers," by Professor H. W. Melville; 11th May, *lecture*, " Some Consequences of Hydrogen Bond Formation in Organic Compounds," by Dr. Wilson Baker; 12th October, *lecture*, " Autoxidation in Relation to Olefinic Structure," by Dr. E. H. Farmer. These meetings were held in the Chemistry Lecture Theatre of the University.

Liverpool. 19th March, at Adelphi Hotel (joint meeting with the Liverpool Section and Food Group of the S.C.I.), *lecture*, " Trends of Agriculture in Relation to Nutrition," by Sir John Russell; 9th April at Reece's Restaurant (joint meeting with the Local Sections of the R.I.C. and the S.C.I. and with the B.A.C.), *lecture*, " The Liquid State," by Dr. E. A. Moelwyn-Hughes; 6th May, in the Muspratt Laboratory (joint meeting with the Local Sections of the R.I.C. and the S.C.I. and with the B.A.C.), *a lecture demonstration* on " Certain Indicators for Volumetric Analysis," by Dr. A. D. Mitchell; 15th September at Reece's Restaurant (joint meeting with the R.I.C., the S.C.I. and the B.A.C.), *talk*, " Problems affecting the Unity of Chemists," by Dr. A. E. Dunstan.

Manchester. 9th January, *lecture*, " Some Applications of Infra-red Spectroscopy," by Dr. H. W. Thompson; 20th February, *lecture*, " The Mechanism of Polymerisation," by Professor H. W. Melville; 8th April, *meeting* for the reading of original papers; 14th May, *Liversidge Lecture*, " Magnetochemistry," by Professor S. Sugden; 25th November, *lecture*, " Modern Technique in Inorganic Chemistry," by Dr. H. J. Emeléus. (These meetings were held in the Chemistry Department of the University.) 15th December, at the College of Technology, exhibition of scientific cinema films. All meetings except that on 8th April were joint meetings with the Manchester Section of the R.I.C.

Newcastle and Durham. 11th November, in the Lecture Theatre of King Edward VII School of Art, King's College, Newcastle (joint meeting with the R.I.C., the S.C.I., Oil and Colour Chemists Association and the B.A.C.), *lecture*, " Plastics," by Mr. I. W. A. Kirkwood.

North Wales. 26th February, in the Chemistry Lecture Theatre of University College of North Wales, Bangor, *lecture*, " Some Aspects of the Chemical Constitution of Milk Fats," by Professor T. P. Hilditch (joint meeting with the University College of North Wales, Bangor, Chemical Society).

Nottingham. 23rd January, *lecture*, " Vitamin A," by Dr. R. A. Morton; 14th May, *lecture*, " Recent Progress in Quantitative X-ray Analysis," by Professor J. M. Robertson; 2nd December, *lecture*, " Some Properties and Reactions of Anhydrous Hydrofluoric Acid," by Dr. H. J. Emeléus. (These lectures were held at University College and the latter two were joint meetings with the University College Physical and Chemical Society.)

St. Andrews and Dundee. 15th April, in the Chemistry Department of University College, Dundee, *Tilden Lecture*, " Recent Developments in the Theory of Reaction Kinetics in Solution," by Mr. R. P. Bell.

Sheffield. 26th February, *Tilden Lecture*, " Aspects of Nucleotide Chemistry," by Professor J. M. Gulland; 14th May, *lecture*, " Modern Technique in Inorganic Chemistry," by Dr. H. J. Emeléus; 10th September, *lecture*, " Some Aspects of Molecular Rearrangement," by Dr. A. W. Chapman; 12th November, *lecture*, " Surface Films," by Professor N. K. Adam. All four lectures held in the Chemistry Lecture Theatre of the University and were joint meetings with the University Chemical Society.

South Wales. 13th February, at University College, Swansea (joint meeting with the University College Swansea Chemical Society), *lecture*, " The Reducibility of Oxides and Sulphides in the Extraction of Metals," by Dr. H. J. T. Ellingham.

The Scope and Limitations of Infra-red Measurements in Chemistry.

THE TILDEN LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON JANUARY 20TH, 1944, AND AT THE ROYAL TECHNICAL COLLEGE, GLASGOW, ON FEBRUARY 18TH, 1944.

By H. W. THOMPSON.

THE regulations of the Tilden lectures lay down that they shall deal with progress in some field of pure or applied chemistry. It seemed to me that the time was opportune to present an account of infra-red measurements, since not only have considerable advances been made in their application to many problems in pure chemistry, but also their significance in industrial work is rapidly becoming widely appreciated.[1] It seems probable that infra-red analysis will soon rank highly for routine and research work in organic chemistry, where its usefulness may at least equal that of ultra-violet spectroscopy.

My subject is singularly fitting for another reason. One of the problems studied by Sir William Tilden was the decomposition of terpenes by heat. He found that when turpentine vapour was passed through a heated iron tube, a mixture of gaseous and condensable hydrocarbons was formed, the analysis of which was difficult. His process has been described as the forerunner of the modern methods of cracking petroleum, and it is in just this field that infra-red spectroscopy has been applied so successfully in recent years. Isoprene was also found by Tilden among the decomposition products of terpenes, and without fully realising what had happened, he observed its polymerisation to form a synthetic rubber. In this field of polymeric chemistry, too, infra-red analysis is proving very valuable.

Comparatively few laboratories in this country have carried out work in the infra-red, and I must therefore state at once that in spite of many striking successes, the use of this technique has certain limitations. For these reasons, it seemed to me better to survey the experimental and theoretical principles of the subject, with typical applications, rather than to deal with more advanced applications to some special group of compounds such as hydrocarbons or polymers of high molecular weight, or with other detailed problems of molecular structure. The topics which I shall discuss fall under two headings, first those dealing with molecular structure and the deduction of chemical data, and secondly, problems in qualitative and quantitative analysis.

The infra-red may be said to extend roughly between the wave-lengths 1μ and $10^4\mu$, or 10^{-4} and 1 cm. This corresponds to a range of frequencies from 3×10^{14} to 3×10^{10} per second. Instead of this absolute unit of frequency, the reciprocal wave-length or wave number is commonly used. Thus a wave-length of 1 cm. corresponds to 1 wave per cm., and one of 10^{-4} cm. to 10^4 wave numbers. A very small part of the above spectral range, namely, that from the visible up to about 1·2μ, can be studied photographically with cyanine-sensitised plates, and by using conventional spectrographs with glass or quartz prisms or finely-ruled diffraction gratings. Between 1μ and 25μ prism spectrometers can be used in which the prism is made of quartz, calcium or lithium fluoride, rock-salt, or potassium halides. The particular characteristics of transmission and dispersive power of these substances make them suitable for different spectral ranges.[2] Unfortunately, natural crystals of rock-salt, fluorite, and sylvine which are of the required size and optical quality are becoming scarce, so the method recently developed in America [3] for producing large blocks of these substances by cooling the molten salts is very valuable. It seems unlikely on theoretical grounds that materials suitable for prisms at wave-lengths beyond 25μ will be discovered, and in this region diffraction gratings have to be used, although these are, of course, used at shorter wave-lengths if higher resolving power is required than can be obtained with a prism spectrometer. The small amount of energy which usually has to be detected makes it desirable to cut the grooves in such gratings so as to obtain favoured angles of reflexion, thereby concentrating the energy in one or two adjacent spectral orders; different " echelette " gratings are then selected for use in particular narrow spectral regions. The manufacture of echelette gratings has hitherto been confined to American laboratories. If these were available from any source in this country, a valuable stimulus would be given to several important fields of research.

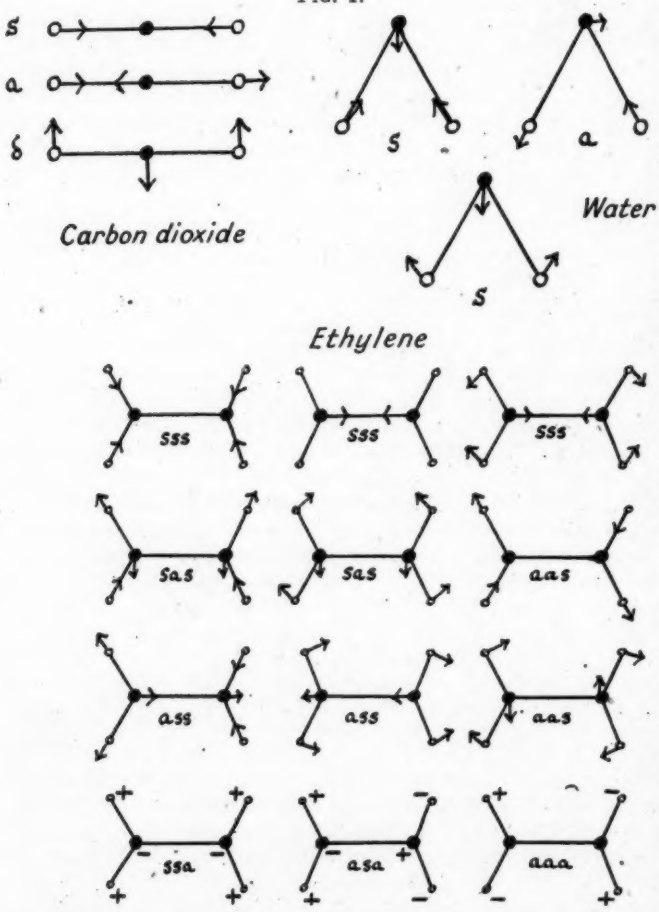
Except in the photographic region around 1μ to which I have just referred, infra-red radiation is usually detected by means of thermoelectric devices. The difficulties of obtaining highly sensitive but stable systems have probably been mainly responsible for the hesitancy with which some workers have entered the field. Very striking advances have now been made, however, in the development of highly sensitive vacuum thermocouples, working with voltage amplifiers of different types. This has led, not only to increased stability of the galvanometric systems, and consequently to increased accuracy, but also to the development of continuously recording automatic infra-red spectrometers which demand no extraordinary manipulative skill. At the present time real progress is being made in this direction, and the study of alternative methods of detection using alternating current bolometers with valve amplifiers may lead to further improvements.

Now, emission spectra in the infra-red have rarely been obtained with sufficient intensity to be measured, and we are nearly always concerned with the absorption spectra, obtained by interposing the substance under investigation between the spectrometer and a source of continuous infra-red emission, such as a Nernst glower or incandescent carborundum rod. In this spectral region energy is absorbed by the molecules as quanta, which cause them to rotate and vibrate. If the molecule, like hydrogen chloride, has a permanent dipole moment, an external field will tend to orient it. A periodically changing electromagnetic field will tend to swing it alternately in opposite directions. Energy can therefore be absorbed to make the molecule rotate.

According to classical theory, a continuous series of energy values will be absorbed, since the molecule will be able to rotate with any frequency. In quantum theory, however, the angular momenta, and therefore the rotational frequencies and values of rotational energy, can only have a series of discrete values, and the frequencies of the radiation absorbed are determined by the quanta of energy according to the well-known relationships of Planck. Diatomic molecules without a permanent dipole moment, such as nitrogen or hydrogen, or spherically symmetrical molecules such as methane, will not absorb rotational quanta.

Similarly, the way in which the dipole moment of a molecule changes during a nuclear vibration will determine whether the particular vibrational quanta are absorbed. If the dipole moment changes during the oscillation, a periodically changing electric field will be set up around the molecule, and its frequency—the same as that of the oscillation—will be absorbed. Here again, homonuclear diatomic molecules will vibrate without the production of a dipole, and will therefore not absorb vibrational quanta. On the other hand, although methane has no permanent dipole moment, it can vibrate in such a way as to produce one, and such a vibration should be absorbed in the infra-red as a fundamental.

FIG. 1.



The quanta of rotational energy, which are determined by the molecular moments of inertia, *i.e.*, by the nuclear masses and internuclear distances, are usually small. The pure rotation spectra therefore lie at low frequencies, that is, at very long wave-lengths, in the region $10^3\mu$ to $10^4\mu$, or 1 to 100 wave numbers. Comparatively little is so far known of these spectra, mainly owing to the technical difficulties in studying this region. With simple diatomic molecules such as the hydrogen halides, the observed spacing of the rotational lines leads to the monent of inertia and hence to the bond length. With polyatomic molecules, the rotational absorption bands are considerably more complicated, and only in a few cases has an analysis been attempted.[4] It may be that developments in the technique of short-wave radio, together with a more accessible supply of coarsely ruled diffraction gratings, will make this an interesting region for future work, particularly for the examination of crystals and solid polymers.

Vibrational quanta, which are determined by the nuclear masses, and the force constants for stretching of bonds and bending of angles, are larger than rotational quanta, the fundamental frequencies varying from about 100 to 4000 cm.$^{-1}$. Accordingly, the fundamentals, lower harmonics, and combination tones are absorbed at shorter wave-lengths, between about 100μ and 1μ. The fact that prism spectrometers cannot be used at wave-lengths longer than 25μ means that vibration frequencies smaller than about 400 cm.$^{-1}$ are not normally measured by infra-red absorption. The absorption of vibrational quanta will usually be accompanied by simultaneous changes in rotational energy. With gases or vapours, these changes give rise to a fine structure of the vibrational absorption bands, measurement of which, as we shall see, has considerable significance. With liquids or solutions, collisions and intermolecular influences lead to the disappearance of the rotational fine structure.

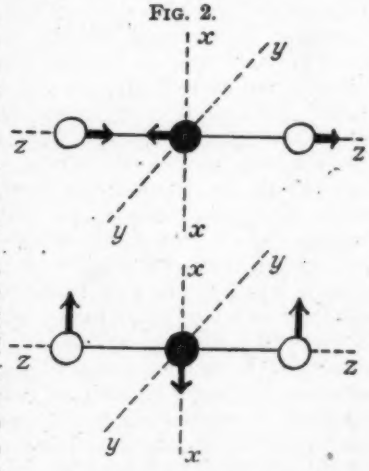
We must now consider the vibrational absorption bands more closely. A rigid molecule of n atoms will have $(3n - 6)$ characteristic normal modes of vibration, in each of which the nuclei are at any instant moving in the same phase. With linear molecules, where there are only two effective axes of rotation, there are $(3n - 5)$ oscillations; on the other hand, if a non-linear molecule can undergo an unrestricted internal rotation about some bond, there will be $(3n - 7)$ vibrations. In simple cases where the molecule has some degree of symmetry, it is possible to specify in a general way the geometrical form of these molecular vibrations. Thus the normal modes of carbon dioxide, water, and ethylene are shown in Fig. 1. The geometrical forms sometimes permit us to speak of "breathing," "rocking," "bending," or "twisting" motions, and in a narrower sense to differentiate between valency vibrations, in which the nuclei move essentially along the valency bonds, and deformations, if the nuclei move essentially at right angles to the bonds. Obviously the sharp distinction

between valency vibrations and deformational modes is strictly valid only in the simplest cases, where the restoring forces opposing stretching and bending differ widely in magnitude. For some purposes of discussion, however, the terminology is useful.

Molecular vibrations can often be characterised in two other, more significant ways. If there is molecular symmetry, any given vibration may be either symmetrical or antisymmetrical with respect to the symmetry property. Thus, the " breathing " vibration of carbon dioxide is symmetrical with respect to the centre of symmetry and the other valency vibration is antisymmetrical. In other cases, where two or more elements of symmetry exist, as with ethylene, a given vibration may be symmetrical to all elements, symmetrical to some and antisymmetrical to others, or antisymmetrical to all. Some vibrations have another property : they are degenerate. Thus the deformational mode of carbon dioxide shown in Fig. 1 is not uniquely defined, since the motions could take place either in the plane of the paper or in a plane perpendicular to it. In certain circumstances this directional equivalence may be removed, so that oscillation is two-fold degenerate.

A consideration of the symmetry of these vibrations shows that they differ characteristically in the way in which the molecular dipole moment changes during the oscillation. Some of the vibrations will involve no change in dipole moment, as in the totally symmetrical modes of ethylene; in others, the direction in which the electric moment changes may be either parallel or perpendicular to some axis of molecular symmetry. As I have already explained, the vibrations which involve no change in dipole moment will be absorbed neither as fundamentals nor as overtones in the infra-red, and in general the intensity of a band will be proportional to the square of the position-rate of change of electric moment during the vibration. It frequently happens therefore that overtones or combinations appear in the infra-red spectrum more strongly than some fundamentals, and in assigning the measured absorption frequencies to particular normal modes, mere intensity will be no rigid guide. Sometimes, those vibrations which are not absorbed as fundamentals appear as combinations with other vibrations, the symmetry properties of the combinations making them permissible. Semi-empirical rules may guide us in the allocation of frequencies to normal modes. Some frequencies which persist through a related series of compounds may be allocated to vibrations of particular groups. In general, too, the motions of lighter nuclei will have higher frequencies than those of heavier nuclei, and comparison of two isotopic molecules in this way may be helpful, particularly those containing hydrogen and deuterium. Also, the deformational modes usually have lower frequencies than the stretching vibrations. It is clear, however, that in no case will mere inspection of the infra-red absorption frequencies lead to an unambiguous assignment of the different magnitudes to the normal modes. In some cases, too, when the harmonic of one vibration is roughly equal in magnitude to another fundamental, resonance occurs, and leads to a pair of new frequencies, one lower and one higher than the larger fundamental. This makes the measured frequencies actually misleading.

FIG. 2.



For many purposes, such as the calculation of thermodynamic properties or force constants, a correct assignment of the fundamentals is essential. Other data, in addition to the above, are therefore required. Most important of these is the Raman spectrum, the great value of which arises because the selection rules which determine whether a particular vibration will be allowed in the Raman or the infra-red spectrum are different. In the Raman effect, vibrations are active if they involve a changing molecular polarisability. Each of the totally symmetrical vibrations of ethylene involves such a changing polarisability, and can therefore appear in the Raman spectrum. The selection rules in any particular case will depend upon the symmetry class to which the molecule belongs. Another useful result is that relatively few combinations are observed in the Raman spectrum. Also, Raman frequencies are found to differ in their degree of polarisation, so that measurement of the latter may enable us to allocate the several magnitudes to vibrations in different symmetry classes. Usually, the more symmetrical vibrations give rise to plane-polarised Raman frequencies, and the less symmetrical to depolarised frequencies.

Some frequencies, *e.g.*, the twisting mode of ethylene, are not found as fundamentals in either the Raman or the infra-red spectra. These can sometimes be determined from a consideration of overtones or combinations, from fluorescence data, or from the measured specific heats. In the last case, the measured specific heat is compared with that calculated by statistical mechanics, all the known frequencies being used. If all the frequencies except one are known, the discrepancy found may lead to an estimate of the missing frequency.

There still remains one other very important method for assigning the vibration frequencies, based upon the analysis of the rotational structure of the infra-red absorption bands.[5] In this way, the molecular structure may also be simultaneously established, since the moments of inertia may be obtained. This can be illustrated with reference to the two vibrations of carbon dioxide which are active in infra-red absorption (Fig. 2). In the antisymmetrical valency vibration the vector corresponding to the change in electric moment is parallel to the molecular axis, and in the deformation it is perpendicular. The molecule can rotate about each of the axes *xx* and *yy*. If it vibrates with the " parallel " change of electric moment, and rotates about *xx*, the electric

moment vector rotates with the vector of angular momentum. The same is true if the rotation occurs about *yy*. This means that rotational energy changes will always be coupled with the vibrational change, and the "parallel" type bands will consist of two groups of rotation lines, the *P* and the *R* branches, corresponding to decrease or increase in rotational quantum number during absorption. Now, if the molecule vibrates with the change of electric moment perpendicular to the axis of symmetry, rotation about *yy* will again involve coupling of the electric moment vector and angular momentum vector, giving *P* and *R* branches; but if rotation occurs about *xx*, the angular momentum vector will rotate in a plane at right angles to the electric moment vector, and independently of it. This means that the perpendicular-type bands will have, in addition to the *P* and *R* branches, a central *Q* line, really a close branch, corresponding to the absorption of the vibration frequency without simultaneous change of rotational quantum number.

The rotational structure of the absorption bands of a linear molecule will therefore reveal at once whether the particular vibration is parallel or perpendicular in type. Conversely, since no other type of molecule gives absorption bands with a central gap due to the missing *Q* branch, the simple *P*–*R* branch type of band is immediate proof of a linear structure. The spacing of the lines in the *P* and the *R* branches of both parallel and perpendicular bands is nearly uniform and equal to $h/4\pi^2 I$, so that I can be determined. We may notice in passing that the separation of lines is inversely proportional to I, so that, as the molecule increases in size, the rotation lines become less well separated. Absorption bands of linear molecules such as carbon dioxide, hydrogen cyanide, and acetylene have been analysed in this way.

Next in simplicity are the non-linear molecules which have an axis of symmetry, such as ammonia, the methyl halides, or methylacetylene, in which $I_A = I_B \neq I_C$. The energy levels of these so-called symmetrical rotators are given by a more complicated expression than that for linear molecules. The parallel type bands have a *P*, *Q*, *R* type structure like that of the perpendicular type bands of a linear molecule, the spacing of the lines in the *P* and the *R* branches being again very close to $h/4\pi^2 I_A$. The perpendicular-type bands have a different structure. There is first a succession of *Q* branches with roughly uniform spacing $(h/4\pi^2)(1/I_C - 1/I_A)$, I_C being the moment of inertia about the symmetry axis. Each of these *Q* branches has alongside it a *P* and an *R* branch, with spacings $h/4\pi^2 I_A$. The *Q* branches usually stand out above the residual background, but the intensity distribution varies according to the relative values of I_A and I_C. Gerhard and Dennison [6] have shown how the intensities vary for different values of the parameters. Once again, however, we can see that, since the spacing between the *Q* branches in a perpendicular band is in many cases relatively large, I_C being smaller than I_A, inspection reveals whether the bands are parallel or perpendicular in type. If it is possible to measure the spacing between the *Q* branches in a perpendicular-type band, and also the spacing between lines in either a *P* or an *R* branch of a parallel band, the values of I_A and I_C are obtained. In this way highly accurate structural data have been obtained for most molecules which are symmetrical rotators, and for some others which deviate only slightly from this. A number of molecules such as the methyl halides have been measured in the photographic infra-red,[7] where overtone and combination frequencies are taken up. In some of these cases, the identity of the spinning hydrogen nuclei within the methyl group leads to characteristic alternations of intensity in the rotation lines.

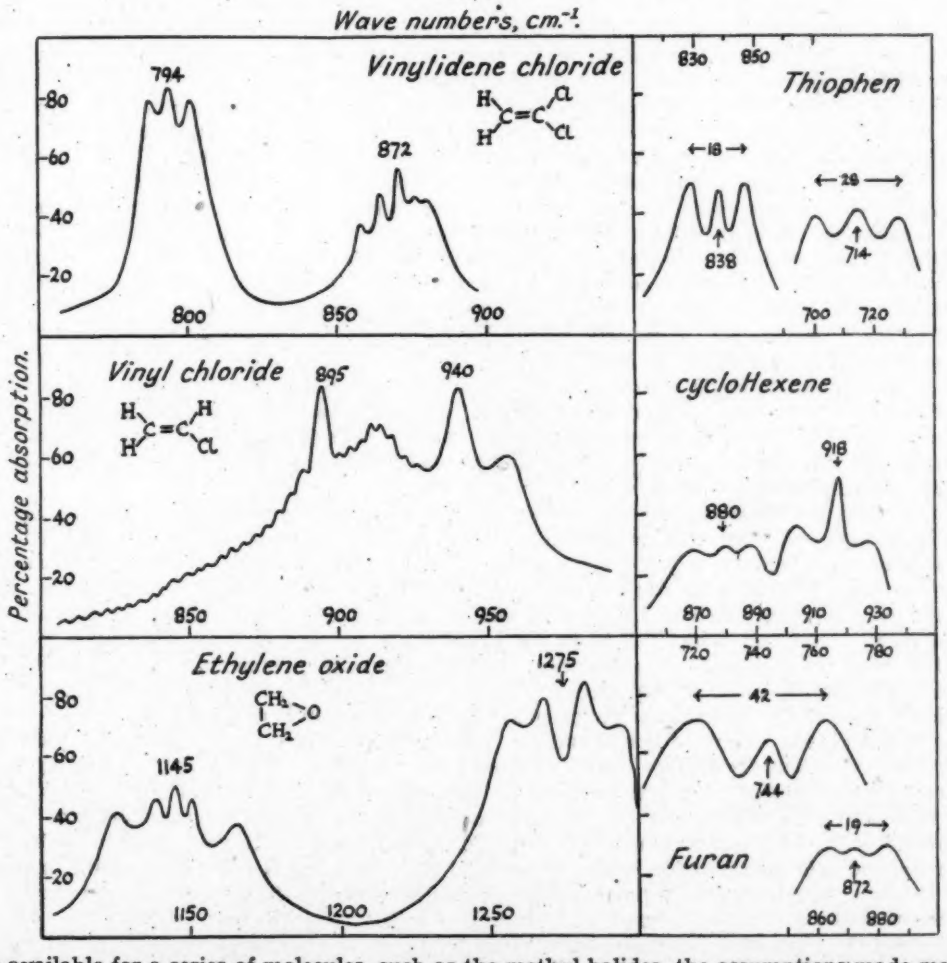
The types of rotational structure so far considered relate to molecules which (*a*) are volatile enough to be studied in the vapour state, (*b*) are small enough to have low moments of inertia and hence resolvable structure, and (*c*) have some symmetry. These restrictions are severe, and the majority of molecules with which the chemist has to deal are excluded. Even when (*b*) or (*c*), or both, do not apply, however, it is often possible to get a partial solution. Thus, if there is some symmetry, but the moments of inertia are large, the envelope of the rotational structure, *i.e.*, the band contour, can be studied. This contour, like the rotational structure itself, varies characteristically with the direction in which the electric moment changes with reference to the axis of symmetry. The spacing between maxima in this contour sometimes leads to an approximate value for one moment of inertia. Thus, Gerhard and Dennison [6] have shown that the spacing between the maxima of the *P* and the *R* branches in parallel-type bands is given by $[S(\beta)/\pi]\sqrt{kT/I_A}$, the quantity $S(\beta)$ being nearly unity but slightly dependent upon the relative value of the two moments of inertia. In these cases, the spectral data really only serve to confirm values for moments of inertia which have been determined in other ways, for when the rotational contour is incompletely resolved, the spacing actually found between sub-maxima will depend upon the exact resolving power used. In any case, however, it is usually possible at least to decide from the contour whether the vibration is parallel or perpendicular in type.

If the molecule under consideration is asymmetrical, $(I_A \neq I_B \neq I_C)$, no general expression can be given for the rotational energy levels, and even when the moments of inertia are small, the fine structure of bands is very complex. Few attempts have yet been made to analyse such bands completely, in spite of the fact that many simple molecules like water, hydrogen sulphide, ethylene, and formaldehyde fall in this group. Here again, some progress can be made by the study of band contours, especially if the molecules do not deviate far from being symmetrical rotators. The molecule will have three principal axes of rotation, the greatest, middle, and least axes of inertia. In any vibration the change of electric moment can be regarded as having components parallel to each of these axes. Badger and Zumwalt [8] have computed the rotational energy levels of molecules in which I_A, I_B, and I_C have different values, both absolutely and relatively, and have thus deduced the approximate rotational contours of bands in which the change of electric moment is parallel to each of the three axes. In practice, any actual band will usually be a hybrid, obtained by compounding the *A*, *B*, and *C* type contours in the correct ratios of intensity, depending upon the relative values of the components of the

electric moment change in the three directions. Although this might be expected to lead to highly complex contours, as indeed it does in some cases, there are many others in which the results are surprisingly simple. In Fig. 3 examples of rotational contours of vibration bands of vinyl chloride, vinylidene chloride, ethylene oxide, *cyclo*hexene, and thiophen are shown.[9] In all these cases, although the moments of inertia cannot be directly determined from the contour, yet an assumed structure can be confirmed, and the particular vibrations can be assigned to different types by using the contour to establish the direction of change of electric moment.

I must at this stage emphasise that even when all three moments of inertia of a molecule can be determined, the whole structure cannot often be fixed, since there will in nearly all cases be more than three parameters, the bond lengths and angles. In order to fix the structure, some of these parameters will have to be assumed. For instance, methyl chloride has only two unique moments of inertia, but three independent parameters, the methyl group angle and two bond lengths. If the angle is assumed to be tetrahedral, the bond lengths follow.

FIG. 3.

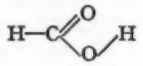
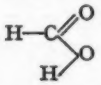


If data are available for a series of molecules, such as the methyl halides, the assumptions made may be substantiated by the self-consistency of the whole series. Another solution may be to use a pair of isotopic molecules. Thus, hydrogen cyanide has only one effective moment of inertia, but two bond lengths. Measurement of the moment of inertia of deuterium cyanide, which has the same bond lengths, will provide a second datum, so that the bond lengths can be deduced.

Another very serious obstacle in the analysis of rotational structure and contours, even with symmetrical molecules, arises from the perturbation of energy levels due to interactions between vibration and rotation. This can be of various types, and results in abnormal spacing of lines, and it unfortunately tends to be specific in different molecules.[10] A particularly interesting interaction of this kind has recently been noticed between two perpendicular vibrations of allene.[11]

Against all these shortcomings, there are, on the other hand, some cases in which an incompletely resolved or analysable rotational structure can still be used to decide between a pair of possible molecular configurations. Thus, hydrogen peroxide has absorption [12] at about 1μ due to an overtone of the O–H stretching frequency. If the molecule had a *cis*-structure, the change in electric moment would be either entirely parallel

or entirely perpendicular to the least axis of inertia, the O–O bond. The observed band has in fact a hybrid structure, which excludes the *cis*-configuration. The *trans*-form is excluded by the value found for the molecular dipole moment. An oblique non-planar configuration is therefore indicated, which is entirely consistent with the details of the spectral data. Similarly, the essentially perpendicular type structure of the O–H (stretching) band of formic acid vapour [13] indicates a *cis*-structure (*a*) rather than the *trans*-form (*b*).

(*a*.)  (*b*.) 

I must now return to the large majority of molecules which are non-volatile or too big to show rotational contour, and for which the only data derivable spectroscopically may be the vibration frequencies. If all these frequencies are known, it may be possible to calculate some useful thermodynamic properties, using the results of statistical mechanics.[14] Each of the properties in which we are interested, such as specific heat, entropy, or free energy, is an explicit function of the partition function $\Sigma e^{-\epsilon_i/kT}$, in which the energy levels ϵ_i are derived from the spectral data. As regards the specific heat, since the contributions from translational and rotational energy terms are constant at most working temperatures, we only have to compute the contribution from vibrational levels $\epsilon_i = h\nu_i$. It must be noted here that, since the greatest contributions come from the lowest frequencies, these must be known accurately, and these are often the most difficult to determine. It is also essential, when degenerate vibrations are present, to allocate them correctly. There is usually no alternative but to assume harmonic character for the vibrations, but this introduces no large error.

Apart from their intrinsic value, specific heats calculated in this manner have led to other knowledge. For instance, a comparison of the calculated and measured values for some molecules revealed discrepancies which were too large to be explained by either experimental or theoretical error.[15] It was then realised that these could be correlated with the phenomenon of internal rotation in molecules. When the potential-energy barrier resisting an internal rotation is high, the molecule will perform a twisting vibration; if the barrier is small, free rotation will occur. There will obviously be intermediate, complex types of motion, the exact nature of which will depend upon the height of the potential barrier and the function relating this potential energy with the azimuthal angle of rotation. The contribution which this torsional motion makes to the specific heat will therefore depend upon many factors. For our present purpose, the important result is that it has been possible to estimate the potential-energy barriers restricting internal rotation about bonds in a series of molecules, and the results suggest that this may be a useful method for discovering something about the forces in molecules between atoms which are not bonded.

If in addition to the vibration frequencies the moments of inertia of a molecule are known, the entropy and free energy can also be calculated. Equilibrium constants can also sometimes be calculated with high accuracy, and others estimated when they are not easily measurable. For this purpose, however, it is usually essential also to have thermochemical data, such as heats of formation, in order to calculate the change in zero-point energy of the reaction being considered. Clearly, with more complex molecules it may be difficult to fix all the frequencies exactly, and only rough values for the moments of inertia may be available. For other reasons, too, the calculations may become less satisfactory. In particular series of compounds, however, it is known that the frequencies fall into groups, and approximations can often be made, especially if the frequencies are high.

Vibration frequencies can also be used to calculate force constants of bonds, accurate values for which would throw much light on the nature of bonds and the distribution of electrons in molecules. Here we have to assume that the vibrations are harmonic, and we must know the form of the function expressing the change of potential energy with nuclear displacements during the oscillation. Application of the Lagrange equations of motion then leads to a determinantal equation, the determinant being of the same order as the number of normal modes. If there is some molecular symmetry, the determinant can be split up so as to obtain equations of lower order, and this simplification is almost essential if the problem is to be manageable, mathematically, at all. In this way, equations are obtained relating the frequencies with the nuclear masses and force constants.

Force constants for stretching of bonds and bending of angles have thus been calculated for some relatively simple molecules.[16] Chemically, the interesting point is to compare the force constants of the same link in a series of different molecules. In some cases the results clearly show the multiple character of bonds and the existence of resonance hybrids.

There are, unfortunately, fundamental difficulties in the extension of such an analysis. The real problem lies in the choice of the correct potential-energy function, since this determines not only the values of the force constants deduced, but also their physical significance. Thus, with a non-linear molecule ABC, if forces are assumed to act solely between atoms which are joined by a conventional bond, the potential function can be assumed to take the form

$$V = \tfrac{1}{2}k_1\Delta^2_{AB} + \tfrac{1}{2}k_2\Delta^2_{BC} + \tfrac{1}{2}k\theta\Delta\theta^2$$

This is called simple valency force field. If, on the other hand, we assume that there are forces between all pairs of atoms, whether bonded or not, we should write

$$V = \tfrac{1}{2}k_1\Delta^2_{AB} + \tfrac{1}{2}k_2\Delta^2_{BC} + \tfrac{1}{2}k_3\Delta^2_{AC}$$

Neither of these functions is completely satisfactory in most cases, in the sense that although a set of values for the constants correctly reproduces some of the frequencies, yet it does not reproduce them all. In order

to obtain consistency, " interaction terms " have to be introduced, corresponding to " cross terms " in the mathematical harmonic form. Even then it seems to be necessary in some cases to introduce more arbitrary constants than the total number of normal modes, which makes the solution impossible. The question arises as to how we are to test the suitability of different functions. We might at first think that the most satisfactory one will be that which reproduces correctly the values for all the fundamental frequencies using the minimum number of arbitrary force constants. This does not seem to be entirely true, for although functions have seemed satisfactory in this respect for one molecule, they have failed to give the frequencies of an isotopic molecule so well. The use of the isotopic effect in testing the function is limited, however, since only with hydrogen and deuterium are the changes in frequencies very large.

To summarise, it seems that progress will have to be made by considering series of related molecules of gradually increasing complexity, introducing into the simple valency force field as many additional constants as may be necessary. It may then be possible to find which type of interaction terms are the most important, and to formulate general rules which throw light on the intramolecular forces.

I can only briefly mention here the empirical relationships which have been suggested between force constants of links and their length.[17] If force constants could be determined accurately for linkages in polyatomic molecules, these relationships might be very useful for estimating bond lengths where other methods fail. Some useful deductions have already been made in this way, but until more data are available it is difficult to say how valuable the method will be. Another interesting chemical problem to which the infra-red data have been applied is the question of optical isomerism in derivatives of ammonia or phosphine, caused by the motion of the apex atom through the plane of the three attached groups. The President discussed this in detail in his address last year.[18]

There is one final application to which reference should be made. It will be clear from what I have said that molecular symmetry plays an important rôle in spectroscopic considerations. We have seen that the symmetry class of a molecule determines the selection rules for the appearance of its vibrations in the Raman and the infra-red spectra. If therefore we examine which frequencies appear in the two types of spectra, which in neither, and which in both, it should be possible to allocate the molecule to a particular symmetry class. This has been attempted in two cases, *viz.*, benzene [18] and *cyclo*hexane.[20] In the former case, the occurrence of a centre of symmetry should forbid the occurrence of the same vibration in both Raman and infra-red spectra. In the latter, the rules will differ characteristically according to whether the molecule has a planar, boat-shaped, or chair-shaped structure. In both cases the results are not very convincing, and this probably arises because the Raman data are normally obtained with the liquids, where distortions may cause the selection rules to break down. Comparisons of this sort using Raman data on vapours might be more informative. I should add here that in the infra-red spectrum, too, differences are often found according to whether the vapour or the liquid is used. This is also presumably to be attributed to alterations in the selection rules caused by molecular distortions.

Now, when a molecule vibrates, it does so as a whole. Strictly speaking, it is incorrect to refer to the vibration of an individual link or group. However, certain linkages and groups retain some individuality, and molecules containing them have frequencies which are little changed in the different molecules. This applies particularly to groups such as O–H, S–H, N–H, or C–H, in which the light atom moves against the much heavier residue, the frequency being therefore hardly affected by variations in the mass of this residue. As Fox and Martin [22] have shown too, the C–H stretching vibrations vary characteristically in frequency with the particular type of C–H linkage, such as $-CH_3$, $>CH_2$, $\equiv C-H$, $>C-H$, or $=CH_2$. Some other bonds, such as C=O, C=C, or C≡N, have valency vibration frequencies which may be slightly affected by neighbouring groups or electronic influences such as conjugation, but generally remain fairly constant. Groups of this kind can therefore be detected by infra-red absorption, and if proper calibrations are made, estimated quantitatively. Conversely, the absence of such a frequency may be taken to indicate interactions, such as intra- or intermolecular association. By this means the existence of hydrogen bonds has been proved in many systems,[23] and more detailed examination may give quantitative data about their nature.

The individuality of linkages tends to disappear when the vibrating nuclei are roughly equal in mass, or the force constants have roughly equal value. In spite of this, however, some nuclear skeletons seem to retain characteristic sets of vibration frequencies in different compounds. For instance, the *tert.*-butyl grouping shows intense absorption in the region of 8μ in a large number of hydrocarbons,[23] arising from vibrations of the carbon skeleton which are little affected by the residue attached to the butyl group; and this absorption is so characteristic that the group could easily be detected in an unknown sample. In some cases, too, the deformational modes preserve their individuality. For example, there is a deformational mode of the methyl group with absorption at about 7·25μ; this can be used for the detection and determination of methyl groups in polythene.[24] Another interesting case is found with the bending mode of the >C—H structure present in different types of olefin.[24] These can be classified as follows:

The infra-red spectra of many compounds of each of these three types reveal that all those in class (2), the vinyl derivatives, have two intense bands at 909 and 990 cm.$^{-1}$; those of type (1) have one at about 890 cm.$^{-1}$; and those of type (3) have one at about 965 cm.$^{-1}$. The corresponding vibration for class (4) is not quite so rigidly defined. When it is required to establish the nature of olefins formed in cracked petroleum or hydrocarbon products, the significance of these results becomes obvious. The spectrum of a sample of Buna 85 synthetic rubber was recently measured (Fig. 4), and showed very intense bands corresponding to types (2) and (3), thus indicating that polymerisation had proceeded both by 1 : 4-addition, giving

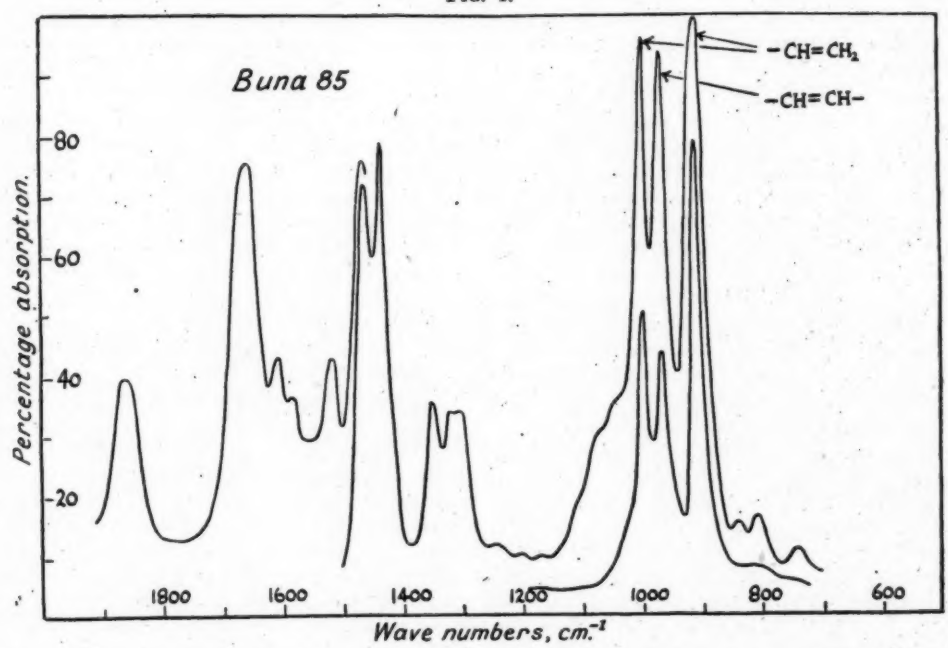
$$—CH_2—CH=CH—CH_2—CH_2—CH=CH—CH_2—$$

and by 1 : 2 addition, giving

$$—CH_2—\underset{\displaystyle CH \\ \| \\ CH_2}{CH}—CH_2—\underset{\displaystyle CH \\ \| \\ CH_2}{CH}—$$

From measurements of intensities, it would be possible to determine the extent to which each type of addition proceeds in a given case. More measurements of this kind are needed on selected series of molecules in order to build up reference data. The quantitative estimation of key groups or parts of a nuclear skeleton requires

FIG. 4.



careful measurement of extinction coefficients, and also fundamental work on the validity of the usually accepted absorption laws.

In polymeric chemistry a variety of problems can be explored successfully, such as the determination of head-to-head or head-to-tail condensation, the relative proportions of different components in an interpolymer, or the position and number of particular groups in long-chain systems. Plane-polarised radiation can also be used in studying oriented solid polymers.[24]

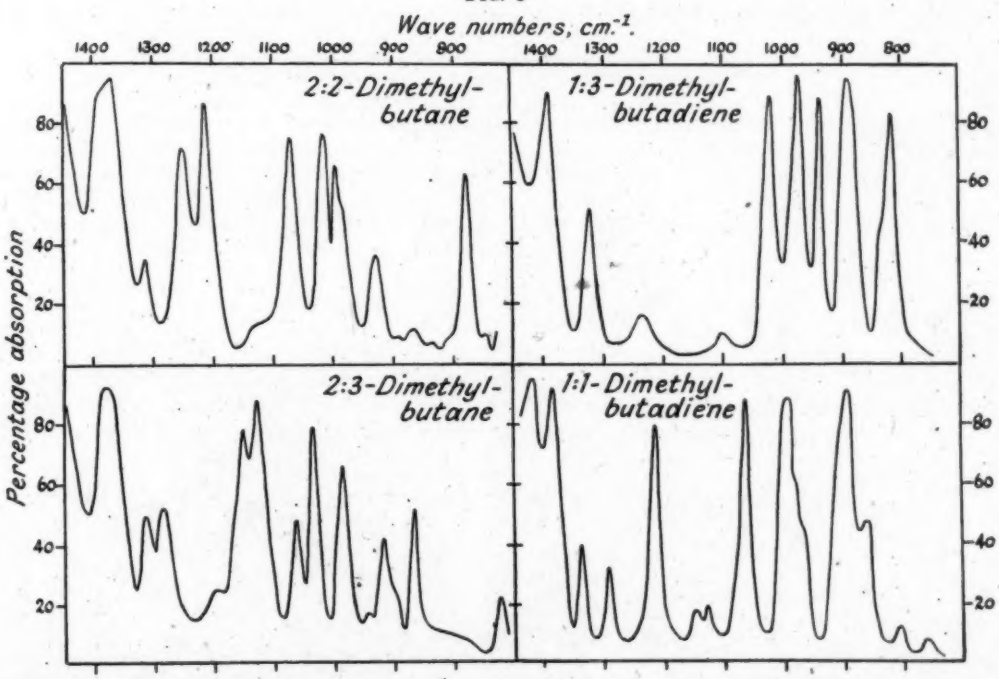
I have just emphasised that, in spite of the individualistic behaviour of some goups in a molecule, a normal vibration really involves the entire molecule. The vibration frequencies are determined by the force constants, nuclear masses, and nuclear configuration. It therefore follows that since no two molecules—except a pair of optical isomers—have the same nuclear configuration, no two molecules can have an identical set of normal frequencies. Related molecules will have some frequencies which may be so nearly equal as to be indistinguishable, but there will be other differences. The infra-red spectrum therefore becomes a fingerprint of the molecule, and when two molecules are present together it should always be possible to identify each of them, unless the spectra are very complex. Analysis for whole molecules in this way has now been developed in many cases, of which I can quote only a few. For example, a mixture of *iso*hexanes can be analysed in this manner, and a similar mixture is that of 1 : 3-dimethyl- with 1 : 1-dimethyl-butadiene (Fig. 5); dodecyl thiocyanate and *iso*thiocyanate show differences in the region of 6μ which make estimation of each in the other possible; mixtures of isomers such as the chlorobenzoic acids, or *o*-, *m*-, and *p*-derivatives can usually be analysed. With series of isomers of this type there appear to be some characteristic displacements of bands in passing along the series, and when more compounds have been measured it should be possible to formulate general

rules from which the important features of unknown spectra can be predicted. Even the spectra of *cis-trans*-isomers show differences in their vibrational spectra, which must arise from the different forms of interaction between groups in the individual molecules. The characteristic differences in the spectra of a polymer and its associated monomer provide a very easy means for following the rate and course of polymerisation processes.

The sensitivity and accuracy obtainable in such analyses vary from one example to another. The method can be based either upon empirical calibration or upon the assumption of the additivity of optical densities. Obviously the circumstances will be most favourable when there is a wide difference in extinction coefficient at any particular key wave-length between the various compounds present.

Analytical work of this kind can usually be carried out rapidly and with very small amounts of the substances concerned, about 0·5 c.c. of a liquid generally sufficing. Indeed, the intensity of infra-red absorption is sometimes so high that extremely thin layers of liquid, say 0·005 mm., have to be used. When we recall that this thickness has to be measured, say, to 1% in a precision cell made from polished rock-salt plates which deteriorate in damp air, it will be realised that a real experimental problem is involved. Work on precision cells is now in progress. An alternative approach would be to use dilute solutions in suitable non-aqueous solvents. Unfortunately, the solvent will also have its own absorption bands, and although in some spectral regions carbon tetrachloride, chloroform, and carbon disulphide have been used with success, solvents

FIG. 5.



are more often a nuisance. In some cases, solid compounds have to be examined which cannot be got into solution at all. A good example of this class is proteins. The technique for handling such substances is not yet fully developed, but some measurements have been made by spreading the powder on a rock-salt plate and moistening it with Nujol or other liquids to reduce scattering. Another limitation to accurate quantitative analysis at present is the difficulty of measuring absorption intensities accurately. Various technical developments seem likely to remove this difficulty. The accurate measurement of extinction coefficients should then lead to other important information about the nature of different types of bond, since it should become possible to correlate absorption intensities with changes in molecular dipole moment.

The diverse applications of which I have spoken illustrate some of the ways in which infra-red measurements have been used in chemistry. In general organic chemistry, other compounds which have been examined [25] include sugars, polycyclic hydrocarbons, celluloses, amino-acids, sterols, vitamins, alkaloids, and hormones. The scope for future investigation is obviously great, though we have seen some limitations. How far the temporary limitations will be permanent must be decided by further work.

References.

[1] Wright, *Ind. Eng. Chem. Anal.*, 1941, **13**, 1; Brattain, *J. Appl. Physics*, 1942, **13**, 699; Barnes, Williams, and Liddel, *Ind. Eng. Chem. Anal.*, 1943, **15**, 83; Barnes, *ibid.*, p. 659.
[2] See Czerny and Röder, *Ergebn. exakt. Naturwiss.*, 1939, 70.
[3] Kremers, *Ind. Eng. Chem. Anal.*, 1940, **32**, 1478.
[4] Randall, *Rev. Mod. Physics*, 1938, **10**, 72.

[8] Dennison, *ibid.*, 1931, **3**, 280; 1940, **12**, 175; Nielsen, *Rep. Progr. Physics*, 1940, **7**, 41; Bartholomé, *Z. Elektrochem.*, 1936, **42**, 341.
[6] *Physical Rev.*, 1933, **43**, 197.
[7] Verleger, *Physikal. Z.*, 1937, **38**, 83.
[8] *J. Chem. Physics*, 1938, **6**, 711.
[9] Thompson, Harris, Torkington, Whiffen, and Temple, to be published.
[10] Nielsen, *Rep. Progr. Physics*, 1940, **7**, 41; Ebers and Nielsen, *J. Chem. Physics*, 1937, **5**, 822; 1938, **6**, 311.
[11] Thompson and Harris, *Trans. Faraday Soc.*, in press.
[12] Zumwalt and Giguère, *J. Chem. Physics*, 1941, **9**, 458.
[13] Bauer and Badger, *ibid.*, 1937, **5**, 852; Thompson, *ibid.*, 1939, **7**, 453.
[14] See Kassel, *Chem. Rev.*, 1936, **18**, 277; Wilson, *ibid.*, 1940, **27**, 17; Zeise, *Z. Elektrochem.*, 1933, **39**, 758, 895; 1934, **40**, 662, 885; *Ann. Reports*, 1935, **32**, 66; 1941, **38**, 46.
[15] *Ibid.*, p. 49.
[16] Thompson and Linnett, J., 1937, 1376; *Ann. Reports*, 1936, **33**, 59; 1941, **38**, 60.
[17] *Ibid.*, 1936, **33**, 59; 1941, **38**, 63.
[18] Mills, J., 1943, 194; Sutherland, Lee, and Wu, *Trans. Faraday Soc.*, 1939, **35**, 1373.
[19] Ingold *et al.*, J., 1936, 912.
[20] Langseth and Bak, *J. Chem. Physics*, 1940, **8**, 403; Rasmussen, *ibid.*, 1943, **11**, 249.
[21] *Proc. Roy. Soc.*, 1938, *A*, **167**, 257; 1940, *A*, **175**, 208.
[22] See *Trans. Faraday Soc.*, 1940, **36**, 871.
[23] Thompson and Sutherland, to be published later.
[24] Thompson and Torkington, unpublished data.
[25] Loufbourow, *Rev. Mod. Physics*, 1940, **12**, 267.

Newer Knowledge of the Biochemistry of the Thyroid Gland.

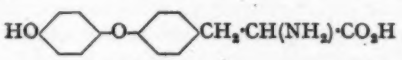
THE PEDLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON MARCH 16TH, 1944, AND AT THE UNIVERSITY, MANCHESTER, ON MARCH 24TH, 1944.

By C. R. HARINGTON, F.R.S.

I PROPOSE to take as the starting point of this lecture the completion of the work which led to the synthetic proof of the constitution of thyroxine. It might have been supposed that after the problems of the isolation of an active principle from the thyroid and of the chemical identification of this principle had been solved, the gland would not have much of new interest to offer to the chemist. It is part of my purpose to show how far such a supposition would have been from the truth and how further work, although perhaps inspired primarily by interest in biological processes, has brought to light matters of interest to the chemist.

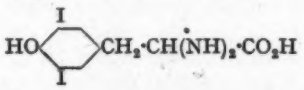
When the constitution of a naturally occurring active principle is explained, the biochemist immediately asks himself from what precursor is it likely to have arisen and what are the processes by which its formation has come about. In the case of thyroxine, indeed, speculation as to the answer to the first of these questions actually preceded the final proof of the constitution and helped to direct synthetic efforts along what proved to be the correct lines.

As soon as the constitution of thyronine or deiodothyroxine had been proved (Harington, 1926) it became

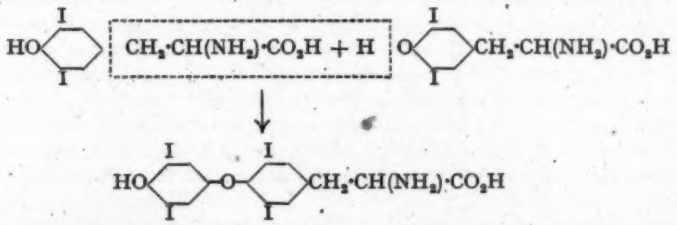


evident that tyrosine was almost certainly a biological precursor of thyroxine. The location of the four iodine atoms of thyroxine in the thyronine molecule could not be achieved with certainty by chemical means and the decision as to which tetraiodothyronine should be selected as a synthetic objective was made principally upon a biological hypothesis.

Until thyroxine was discovered and shown to be an iodine-containing amino-acid, only one other natural compound of this type was known, namely, 3 : 5-di-iodotyrosine :



Now just as thyronine could be regarded as a condensation product of two molecules of tyrosine with loss of one side chain, so thyroxine might reasonably be derived by a similar reaction from 3 : 5-di-iodotyrosine; if this were to happen, the compound produced would be 3 : 5 : 3′ : 5′-tetraiodothyronine :



The synthesis of the latter substance and the proof of its identity with thyroxine (Harington and Barger, 1927) provided circumstantial evidence of the validity of the biological hypothesis, and made it all the more desirable that direct experimental evidence should be sought.

Clearly a fundamental requirement of the theory that the biosynthesis of thyroxine proceeds through 3 : 5-di-iodotyrosine is the demonstration of the presence of the latter compound in the animal body; there is no place in the body where iodine occurs in any significant concentration except in the thyroid itself, and it was therefore in this organ that di-iodotyrosine must be sought.

Earlier work had shown that the whole of the iodine in the thyroid was in firm organic combination and that it was confined to the protein thyroglobulin which constituted the characteristic colloid material of the gland. On the other hand, even with improved methods of isolation it was not possible to account for a very large proportion of the total iodine of the thyroid in terms of thyroxine. Furthermore, in the course of the study of the isolation of thyroxine it became apparent that the iodine of the thyroid was easily separable into two distinct fractions characterised by their widely different solubilities at about pH 5. Such a separation could be effected by mild alkaline hydrolysis, as in the ordinary process of isolation of thyroxine, or by the early stages of enzymic breakdown of thyroglobulin. Of these two fractions, only that which was insoluble at pH 5 exhibited physiological activity and served as a source of thyroxine, in spite of the fact that most of the iodine in the soluble fraction remained in organic combination.

These facts then were known at the time when thyroxine was synthesised, and they carried the strong suggestion that it was among the acid-soluble hydrolytic products of thyroglobulin that di-iodotyrosine would

most probably be found. This acid-soluble fraction of the hydrolytic products was therefore subjected to complete hydrolysis with alkali, and a systematic search was made for di-iodotyrosine which was guided by the known properties of this amino-acid. Detailed description of the methods employed is unnecessary; it will suffice to say that the search was successful, di-iodotyrosine being identified among the products of hydrolysis without much difficulty (Harington and Randall, 1929).

The observation just described thus afforded a significant piece of qualitative evidence in favour of the biogenetic hypothesis under consideration. It seemed worth while, however, to press the matter a little further, and to attempt to make so far as possible a quantitative allocation of the iodine of the thyroid to thyroxine and di-iodotyrosine respectively; not only would this indicate the approximate proportions in which the two compounds occurred in the thyroid, but it might also be expected to reveal the existence of other organic iodine compounds if such occurred in the thyroid. With this end in view a quantity of desiccated thyroid was submitted to the step-wise hydrolytic process which had been employed for the isolation both of thyroxine and of di-iodotyrosine. At the early stage of mild hydrolysis the two main fractions, acid-insoluble and acid-soluble, were separated as sharply as possible, and from these fractions were isolated thyroxine and di-iodotyrosine respectively. Every step of the process was accompanied by an iodine analysis in order that any significant loss of iodine should be observed. The result of this experiment was to show that although the over-all losses of iodine were considerable, only one step was accompanied by a loss greater than could reasonably be regarded as due to the nature of the manipulation. This exceptional loss occurred at the stage when the hydrolytic products were subjected to intensive alkaline hydrolysis; after this operation approximately one third of the iodine appeared in the form of iodide in the acid-soluble fraction and a considerably smaller proportion appeared similarly in the acid-insoluble fraction. It was, however, demonstrable by experiments on the pure compounds that intensive alkaline hydrolysis caused some decomposition with liberation of iodine in both cases, the destruction being relatively greater with di-iodotyrosine than with thyroxine. This being so, it was unnecessary to assume that the iodine appearing as iodide at the stage of intensive hydrolysis originated from compounds other than thyroxine and di-iodotyrosine, and indeed the upshot of the whole experiment was to indicate clearly that these two compounds accounted between them for the whole of the iodine of the thyroid; moreover it appeared that they were present in somewhat similar amounts, di-iodotyrosine slightly preponderating. Thus not only have we the proof that di-iodotyrosine is a constituent of the thyroid, but we see that it is quantitatively the most important iodine-containing compound which occurs therein.

The fact that neither thyroxine nor di-iodotyrosine could be isolated from thyroglobulin except after a process of drastic hydrolysis, coupled with the observation that both compounds thus isolated were obtained in the racemic condition, gave a strong indication that they must originally have been present as constituent amino-acids of the thyroglobulin. Direct proof of this supposition was afforded by the results of enzymic degradation of thyroglobulin (Harington and Salter, 1930). By a laborious process involving successive digestion with pepsin, trypsin and finally a peptidase-containing extract of intestinal mucosa it was possible to isolate a small yield of thyroxine. Analysis of the intermediate fractions obtained for iodine and for total and amino-nitrogen made it quite clear that the process of isolation consisted of the enzymic breakdown of peptide chains containing thyroxine as a constituent amino-acid; moreover the thyroxine finally isolated proved to be optically active; similar evidence was later obtained in respect of di-iodotyrosine.

I have mentioned this proof that thyroxine and di-iodotyrosine occur naturally as constituent amino-acids of thyroglobulin, not because it has a direct bearing on the problem of the biogenesis of thyroxine, but because the availability of natural optically active thyroxine which resulted from it made possible a further chemical attack on this problem.

The optically active isomerides of thyroxine had indeed been prepared by resolution of the *dl*-compound (Harington, 1928) (or more precisely of *dl*-3 : 5-di-iodothyronine, followed by iodination of the enantiomorphs) before natural thyroxine had been isolated as described. Although, however, the lævorotatory synthetic isomeride exhibited a higher degree of physiological activity than the dextrorotatory compound, the difference was not very great, and complete certainty as to which was the natural compound had to await the isolation of the latter by methods which did not involve racemisation; when this was accomplished the natural compound turned out in fact to be lævorotatory as had been anticipated from the biological activity.

The optical rotation of natural thyroxine having thus been established, it was clear that if thyroxine could be synthesised from natural *l*-tyrosine by a series of reactions which did not involve the possibility of an optical inversion the product obtained should be identical with natural thyroxine if the biogenetic hypothesis were correct. At the time of which I am speaking the possibility of such a direct synthesis of thyroxine from tyrosine was not in sight, but there remained an indirect method of attack of the problem; it appeared that it might be possible to synthesise thyronine from tyrosine; if this could be accomplished, the optical rotation of the product could be compared with that of a sample of thyronine prepared by the catalytic deiodination of natural thyroxine.

The method by which this object was achieved is as follows (Canzanelli, Harington, and Randall, 1934). The ethyl ester of *N*-benzoyl-*l*-tyrosine was condensed with 3 : 4 : 5-tri-iodonitrobenzene by boiling in methyl ethyl ketone solution with potassium carbonate to give ethyl α-benzamido-β-[4-(3′ : 5′-di-iodo-4′-nitrophenoxy)-phenyl]propionate; the object of employing 3 : 4 : 5-tri-iodonitrobenzene instead of the more obvious *p*-iodonitrobenzene is simply to improve the yield in the condensation; the subsequent removal of the 3′ : 5′-iodine

atoms can be effected in quantitative yield and without difficulty. The ester thus obtained was hydrolysed to the free acid, which in turn was reduced with ferrous sulphate and baryta to the corresponding amino-compound; the latter was deiodinated by catalytic hydrogenation in the presence of palladised calcium carbonate and the resulting iodine-free acid was converted into *N*-benzoylthyronine by diazotisation, followed by boiling of the aqueous solution of the diazonium salt; thyronine obtained by hydrolysis of the *N*-benzoyl derivative had $[\alpha]_{5461} + 13{\cdot}3°$. A sample of thyronine, which was obtained, on the other hand, by catalytic deiodination of natural *l*-thyroxine had $[\alpha]_{5461} + 12{\cdot}2°$. It is clear, therefore, that the preparations of thyronine obtained from natural tyrosine and from natural thyroxine are configuratively identical, from which it follows that natural tyrosine and natural thyroxine are configuratively related.

It will be seen from what I have to say later that a more direct chemical proof of the configurative relationship of tyrosine and thyroxine has recently become available. The establishment of the configurative relationship, however, by the indirect method which I have described sufficed to bring strong chemical support to the idea that tyrosine was in fact the biological precursor of thyroxine.

In thinking of the biosynthesis of thyroxine from tyrosine it is necessary to consider the reaction in two phases, the first consisting of the iodination of tyrosine and the second of the coupling of two molecules of the latter to give thyroxine. As to the first phase there is little to be said, except that it must be presumed to occur in the thyroid gland and that it must involve an oxidative system which will liberate iodine from iodide, which is the form in which iodine taken into the body reaches the thyroid. It has already been stated that the thyroid gland is the only situation in the body where iodine occurs in significant concentration. The avidity of the thyroid for iodine is indeed very striking; for instance, if a dose of 50 mg. of potassium iodide is administered to a dog, 18·5% of the iodine can subsequently be recovered from the thyroid although the latter represents less than 0·15% of the total body weight; moreover, if the animal receiving the iodine has previously been in a state of iodine deficiency, the administration of iodide results in rapid storage of colloid (thyroglobulin) and in enhancement of the physiological activity of the gland. It is clear, therefore, that iodine introduced into the body as iodide is specifically taken up by the thyroid and there enters into organic combination which may lead to the production of the active principle; whatever the later stages of the synthesis of thyroxine may be, the first event must be substitution of the iodine in the molecule of an organic compound, and such substitution can only occur after oxidation of the iodide. Direct evidence that the first reaction which occurs is in fact the formation of di-iodotyrosine has recently been provided by the work of two groups of American investigators (Perlman *et al.*, 1941, a & b; Morton and Chaikoff, 1943; Mann, Leblond, and Warren, 1942), who have employed radioactive iodine for the study of the process. Immediately after the administration of iodide containing a proportion of radioactive iodine, part of the radioactivity is found in iodide in the thyroid; a few hours later radioactivity appears in the fraction of the hydrolytic products of the thyroid which contains di-iodotyrosine, and still later in the fraction containing thyroxine, whilst at the same time the proportion of iodine present as iodide diminishes. In addition to the experiments on the intact animal the metabolism of iodine has been studied in thyroid slices. By the use of radio-iodine the same result has been demonstrated, namely, rapid conversion of iodide into di-iodotyrosine, followed by later formation of thyroxine.

So far as the general thesis is concerned, therefore, we see that there is now an impressive body of evidence, both chemical and biochemical, that thyroxine is in fact formed in the body from tyrosine and iodide through the intermediate stage of di-iodotyrosine. The details of the biological process remain to be elucidated; observations on the effect of typical enzyme inhibitors (Schachner, Franklin, and Chaikoff, 1943) indicate that it is in part at least controlled by an oxidising enzyme system; there is, however, nothing to show whether one and the same enzyme catalyses both phases of the reaction, whether there are separate enzyme systems which catalyse the oxidation of iodide required for iodination of tyrosine and the coupling of two molecules of di-iodotyrosine to give thyroxine, or whether, by analogy with the formation of melanin from tyrosine by tyrosinase, only one phase of the over-all reaction is enzymic in character. I do not propose to pursue these questions further on this occasion; rather do I wish to direct attention to the chemistry of the second part of the reaction, namely, the conversion of di-iodotyrosine into thyroxine.

The first aspect of this matter which I wish to discuss concerns the action of iodine on proteins. When it was first discovered that the physiological activity of the thyroid was associated with iodine and that this iodine was organically bound in thyroglobulin, a discovery which preceded the isolation of thyroxine by 20 years, interest was at once aroused in the possibility of obtaining products having similar physiological properties by treatment of other proteins with iodine. Many investigations were made in which proteins were treated with iodine under various conditions of pH and temperature. In all cases products were obtained which contained more or less iodine in organic combination, but in the earlier work no indication, or only doubtful indications, of physiological activity were observed. Study of the chemistry of the iodinated proteins did, however, reveal certain points of interest. The most significant observation from the point of view of the present discussion was that of Oswald (1910), who found that iodination of albumin, gliadin and casein in alkaline solution gave products from which he was able to isolate 3 : 5-di-iodotyrosine; this revealed the predominant importance of tyrosine as an iodine-binding constituent of the protein molecule. No pure iodine-containing compound other than di-iodotyrosine could be isolated from iodinated proteins, but in some cases there was evidence that the total amount of iodine bound was more than could be accounted for by the tyrosine content of the protein. A plausible explanation of this observation was offered by the dis-

covery of Pauly (1910) that the iminazole ring is readily iodinated, and that this was the true explanation was indicated by the fact that the discrepancy between the iodine bound and the tyrosine content was greatest in proteins such as globin which contained a large proportion of histidine. With increasing knowledge of the iodination of tyrosine it has been shown in recent years that, except when an unusually large amount of histidine is present, it is possible by choosing the proper conditions almost to titrate the tyrosine in a protein with iodine and to obtain a product in which the combined iodine is stoicheiometrically equivalent to the tyrosine, assuming conversion of the latter into di-iodotyrosine. This reaction has found several useful applications; it has been used by Neuberger to expose the rôle of tyrosine in the base-binding properties of zein and insulin (Neuberger, 1934; Harington and Neuberger, 1936); it has revealed the essential character of the tyrosine groups for the specific activities of insulin (Harington and Neuberger, 1936) and pepsin (Herriott, 1941—42), and it has found wide application in immunochemical studies.

It will be seen that the early disappointment regarding the production of physiologically active substances by iodination of proteins led the further study of this reaction into other channels, and, although occasional claims to have produced physiological activity were made, serious attention was not given to this part of the problem until comparatively recently when, in a series of papers, Abelin (1933, 1934, 1936, 1938) claimed to obtain physiologically active iodinated proteins from which, by alkaline hydrolysis, he could separate fractions having the general physical and chemical properties of thyroxine; in only one instance, however, was a crystalline substance having physiological activity isolated and this was not satisfactorily characterised. The matter therefore remained in doubt and it was not until 1939 that a paper was published by Ludwig and von Mutzenbecher which changed the whole situation. These workers published a detailed description of a method for the iodination of casein and other proteins to give products which were not only physiologically active themselves but from which it was actually possible to isolate thyroxine. I must confess that this result seemed to me at first to be so surprising that I was not prepared to accept it until I had repeated it in my own laboratory (Harington and Pitt-Rivers, 1939); I had, however, no difficulty at all in convincing myself that the observation was correct.

There were of course two possible explanations of the formation of thyroxine during iodination of a protein, namely, (1) that thyronine was already present in the protein molecule and was directly iodinated, and (2) that the di-iodotyrosine which must have been formed had in part undergone secondary conversion into thyroxine. Of these two explanations the second seemed for many reasons to be the more acceptable. In the first place all the evidence pointing towards the biological formation of thyroxine from tyrosine which I have recounted was available except for the experiments with radio-iodine; secondly, the direct iodination of thyronine to thyroxine had previously been attempted on many occasions and under widely different conditions and had entirely failed. Moreover the essential feature of the process of Ludwig and von Mutzenbecher appeared to be that the iodination was carried out under conditions which might be expected to favour oxidative side-reactions, namely, in dilute alkaline solution at a slightly elevated temperature; in this respect their experiments contrasted with most modern work on the iodination of proteins, which, as we have seen, was directed towards quantitative iodination of the tyrosine. Assuming the hypothetical coupling of two molecules of di-iodotyrosine to give one of thyroxine to be an oxidative process, it seemed reasonable to suppose that hypoiodite, formed on addition of iodine to the alkaline solution, might be the oxidising agent responsible. There were, however, certain features of the reaction which were difficult to understand on the simple hypothesis just outlined. For instance, the proportion of iodine added appeared to be fairly critical and was less than that which gave products with maximal iodine content; such products in fact showed little or no physiological activity and failed to yield any thyroxine. Moreover, if the picture which has been given above were correct, it might have been supposed that the yield of thyroxine obtainable from the iodinated product would bear a direct relationship to the tyrosine content of the original protein; this, however, was not the case, silk fibroin, for instance, which contains a very high proportion of tyrosine, failing to give any active product. The reaction is thus obviously a complex one in which the structure of the protein is involved. The work of Ludwig and von Mutzenbecher has considerable practical importance, since it offers the possibility of the cheap and easy preparation in large quantities of products having the specific physiological properties of thyroid gland. This being so, it is not surprising that the reaction has been studied extensively both in this country (unpublished work in my own laboratory) and in America (Reineke and Turner, 1942); the large amount of work which has been carried out has, however, done little but confirm the original observation, extend it to other proteins and define more sharply the conditions which must be observed if optimal yields of active material are to be obtained; the essential chemistry of the process remains obscure. The establishment of the possibility of forming thyroxine by iodination of proteins, interesting as it is, does not therefore take us much further in the detailed explanation of the process.

About a year after the publication of the work on iodinated proteins, however, another paper appeared from von Mutzenbecher (1939) in which he described the formation of thyroxine during prolonged incubation of di-iodotyrosine in slightly alkaline solution. The proportion of thyroxine thus formed was so minute that a faint suspicion attached to the observation in so far as it applied to di-iodotyrosine derived from natural tyrosine; before long, however, this doubt was removed by the repetition of the experiment in America (Block, 1940) with di-iodotyrosine of synthetic origin, the yield of thyroxine being similar to that obtained by von Mutzenbecher. This new observation of von Mutzenbecher seemed to open up fresh possibilities for the study of the chemical transformation of di-iodotyrosine into thyroxine. In von Mutzenbecher's experi-

ment the formation of thyroxine was accompanied by liberation of a significant amount of iodine, which, at the alkaline reaction employed, must have formed some hypoiodite; here again, therefore, as in the protein iodination experiments, we have the suggestion that the oxidising action of hypoiodite may be concerned in the transformation. This suggestion was taken up by T. B. Johnson (Johnson and Tewkesbury, 1942) in America, who propounded a theory of the mechanism of coupling of two molecules of di-iodotyrosine into the details of which I shall go later; he also claimed that the addition of hypoiodite to the solution of di-iodotyrosine slightly increased the yield of thyroxine, but he gave no actual figures in support of this claim.

Assuming the truth of the suggestion that hypoiodite was indeed the effective agent both in the formation of thyroxine in iodinated proteins and in the direct conversion of di-iodotyrosine into thyroxine, it seemed to us that a study of the action of other mild oxidising agents in bringing about the latter reaction might be profitable. Johnson's theory was based on the Pummerer oxidation of phenols in which the oxidising agent employed was potassium ferricyanide; the obvious first step, therefore, was to examine the action of the latter on di-iodotyrosine; in none of a number of experiments, however, was any indication obtained of the formation of thyroxine; extensive disruption of the di-iodotyrosine occurred under the mildest conditions which could be devised.

From potassium ferricyanide we turned to hydrogen peroxide, a reagent which, as is well known, frequently resembles biological oxidation systems in the reactions which it brings about. At first we employed the hydrogen peroxide in slightly alkaline solution at 37°; the mixture was incubated for various times and worked up for thyroxine by the method used by von Mutzenbecher. In this way we were able to observe at least an acceleration of the formation of thyroxine, although the yield remained minute and of the same order as that which resulted from the more prolonged incubation of an alkaline solution of di-iodotyrosine without added oxidising agent. We next found, somewhat to our surprise, that the yields of thyroxine were significantly improved by employing more drastic conditions of oxidation with larger amounts of peroxide at a higher temperature. We also found that the reaction was influenced by the pH of the solutions, rough orientating experiments indicating an optimum at about pH 10.

So long as the experiments were carried out in aqueous solution, the crude thyroxine being isolated at the end of the reaction by precipitation with acid, the yields remained very small. The dark colour of the oxidised solution and the large proportion of tarry by-products formed indicated that extensive oxidative destruction was taking place, and indeed it appeared likely that much of the thyroxine which might be formed would undergo secondary oxidation under the conditions employed. We therefore adopted a technique which we hoped would protect the thyroxine by removing it as it was formed from further contact with the oxidising agent. It was observed some years ago by Leland and Foster (1932) that, when an alkaline solution of a mixture of thyroxine and di-iodotyrosine was shaken with butyl alcohol, 92% of the thyroxine passed into the alcohol whilst over 97% of the di-iodotyrosine remained in the aqueous phase; the experiments of Leland and Foster were actually carried out with solutions of N- or 2N-sodium hydroxide, but the distribution coefficients presumably depend upon the relative solubilities of the salts of the two amino-acids and do in fact bear a similar relation to one another at pH 9—10 (the pH of our oxidation), although the separation is not so sharp as in more strongly alkaline solutions. It seemed therefore that, if the solution of di-iodotyrosine being oxidised were to be shaken with butyl alcohol, the thyroxine should pass into the latter and there be relatively protected. This process has indeed met with some success in our hands and has led to significantly increased yields of thyroxine.

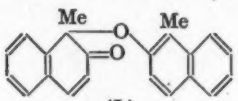
In a typical experiment of this kind 0·05 g.-mol. of di-iodotyrosine was dissolved in 95 c.c. of N-sodium hydroxide to give a solution of about pH 10; 100 c.c. of butyl alcohol were added and the mixture was heated on the steam-bath; 20 vol. hydrogen peroxide was then added in 10 c.c. portions with constant shaking and after each five additions the butyl alcohol was separated and replaced with fresh solvent; the reaction was kept alkaline to phenolphthalein by addition of alkali as necessary. In all some thirty additions of hydrogen peroxide were made over 5—6 hours, representing a very large excess (8 atomic equivs.), but naturally under the conditions of the experiment much of the peroxide decomposed immediately. The thyroxine was isolated from the butyl alcohol extracts by a method which need not be described in detail. The pure thyroxine ultimately obtained amounted to 319 mg., representing a gross yield of 1·36% and a net yield of 3·4% after allowing for the unchanged di-iodotyrosine which could be recovered. This compares with a gross yield of 0·23% obtained by von Mutzenbecher; his net yield is not known, since figures are not given for the recovery of di-iodotyrosine.

It is not to be supposed that the experimental conditions which I have described necessarily represent the best that can be found for the conversion of di-iodotyrosine into thyroxine; indeed it seems improbable that this should be so. It is, however, clear that oxidation with hydrogen peroxide brings about with much greater rapidity and in much greater yield the same transformation which occurs on incubating di-iodotyrosine in alkaline solution. One point of interest which may be mentioned at this stage is that the thyroxine which is formed from di-iodotyrosine (itself prepared from natural *l*-tyrosine) is lævorotatory and therefore identical with natural thyroxine isolated from the thyroid by enzymic hydrolysis. This is the piece of direct chemical evidence to which I referred earlier, finally proving the configurative relationship of natural thyroxine and natural tyrosine.

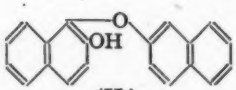
As has already been noted, the oxidation of di-iodotyrosine with hydrogen peroxide is accompanied by extensive decomposition with formation of tarry by-products; oxidative disruption of the di-iodotyrosine

is also indicated by the formation of acid which occurs during the reaction. A search has been started among the by-products in the hope that a compound might be found which would throw light on the course which the reaction follows; however, in spite of the fact that several pure substances have been isolated in minute yield, none has yet been identified which is useful for this purpose. Anything further therefore which may be said about the chemistry of the conversion of di-iodotyrosine into thyroxine must be of a theoretical and speculative nature; I am encouraged to enter on such speculation not only by the intrinsic chemical interest of the reaction but by the terms of reference of the Pedler Lecture which state that " the lecture should indicate directions in which further work is required."

Mention has already been made of the theory propounded by T. B. Johnson. This is based on the work of Pummerer on the oxidation of phenols in alkaline solution with potassium ferricyanide. Pummerer's earlier experiments were carried out for the most part with naphthol derivatives. He observed (Pummerer, 1919; Pummerer and Cherbuliez, 1919) that the dehydrogenation of a compound such as 1-methyl-2-naphthol led to an intermediate which had the empirical formula of di-(1-methylnaphthyl) peroxide; this intermediate did not, however, behave like a peroxide and was later formulated on good evidence as having the structure (I). Structures of type (I) were assumed by Pummerer to be formed from the interaction of free radicals (Pummerer and Frankfurter, 1914; Pummerer and Cherbuliez, 1914), into which they themselves indeed readily dissociated; in the more complicated cases the free radicals showed exceptional stability. The best explanation of the formation of structure (I) and of other reactions observed was given by the assumption that the radicals



(I.)



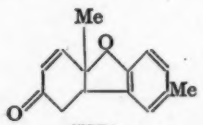
(II.)

were of two types, one, as we should now say, having the odd electron on the carbon atom carrying the methyl group and the other having the odd electron on the oxygen atom. Interaction of the two different radicals would give (I) or its analogue, whilst interaction of two radicals of the first type would give a dinaphthyl such as was already known to arise from the oxidation of naphthols under certain conditions.

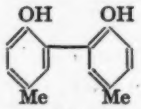
In the case of β-naphthol itself the intermediate of type (I) is able to stabilise itself by internal rearrangement and the product of dehydrogenation is 2-hydroxy-1 : 2′-dinaphthyl ether (II). It may be noted, in view of what is to be said later, that in a phenol carrying substituents in the *o*-positions, similar stabilisation with ether formation may be expected to occur in the *p*-position if this is free.

That peroxide formation does in fact occur during the dehydrogenation reaction was demonstrated by Pummerer (Pummerer and Rieche, 1926), when he isolated a mixed peroxide by oxidation of hydroxynaphthylene oxide; it was only in this instance, however, that a peroxide could be obtained and it was extremely unstable; Pummerer regarded the peroxide as the initial intermediate in the production of compounds of type (I); it could equally well be the product of reaction of two free radicals having the odd electron on the oxygen atom.

The example taken by Johnson for an analogy in considering the conversion of di-iodotyrosine into thyroxine is the oxidation of *p*-cresol. In Pummerer's hands (Pummerer *et al.*, 1922, 1925) this led to the formation of the ketotetrahydrobenzofuran derivative (III) and to the di-*p*-cresol (IV) as main products:

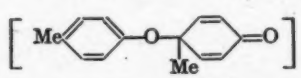


(III.)



(IV.)

In the light of his earlier work the formation of (III) was explained as proceeding through the intermediate compound (V):

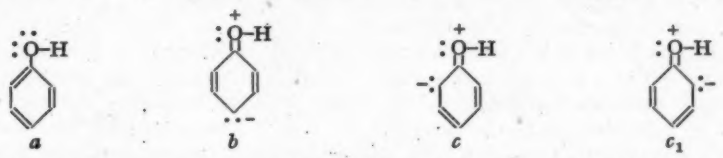
(V.) 

Johnson points out that, if a similar course of reactions is assumed for the oxidation of di-iodotyrosine, the rearrangement of the intermediate quinonoid compound to the stable tetrahydrobenzofuran structure cannot take place, being prevented by the presence of the iodine atoms *ortho* to the phenolic group. If, therefore, an intermediate product of this type is formed from di-iodotyrosine, the molecule may stabilise itself in one of two ways, both of which involve the loss of the side chain attached to the same carbon atom as the ether oxygen; this side chain will split off as a dehydroalanine residue, which either may be hydrolysed to pyruvic acid and ammonia or may add the elements of water to give serine; Johnson states that he was able to identify pyruvic acid and ammonia among the oxidation products and he therefore favours the first mechanism. The identification of the pyruvic acid in Johnson's experiments was not, however, very conclusive, and plausible as his theory is it cannot therefore be said to rest on a very secure foundation. Further evidence which was foreshadowed in his communication has not yet been forthcoming.

Whilst it remains probable, therefore, that the mechanism proposed by Johnson gives a generally correct

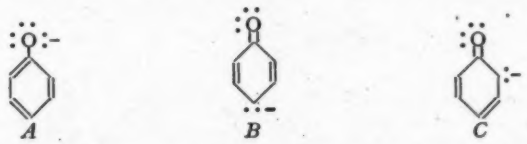
picture of the course of events in the transformation of di-iodotyrosine into thyroxine, it seems worth while to analyse the reaction somewhat more closely, and particularly to see whether useful indications may be obtained by application of accepted theories of resonance structure in so far as they relate to phenols and phenoxide ions. We may first consider this in relation to the Pummerer reaction.

The large magnitude of the acid dissociation constant of a phenol compared with that of an aliphatic alcohol is attributed to resonance of the normal structure *a* with the three structures *b*, *c*, and c_1 :



a *b* *c* c_1

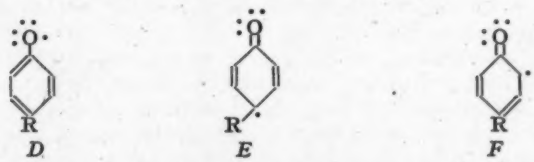
For the purpose of the subsequent argument *c* and c_1 are identical and will be treated as one. In the case of the phenols themselves the contributions of structures *b* and *c* to the normal state of the molecule are small,



A *B* *C*

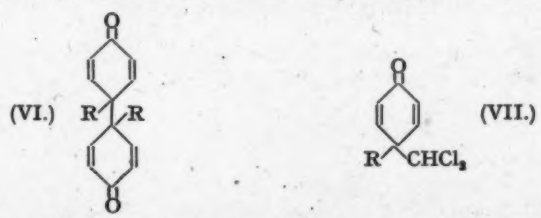
but in the corresponding phenoxide ions, *A*, *B*, and *C*, the contributions of *B* and *C* are greater, since the resonance forms of the ions differ only in the position of the negative charge, whilst the resonance forms of the phenols have separated charges and are therefore less stable. This point should be borne in mind in relation to the fact already stated that the transformation of di-iodotyrosine into thyroxine occurs most readily at a pH at which the phenolic group will be completely dissociated. The same conditions obtain in Pummerer's oxidation of *p*-cresol, which is carried out in sodium carbonate solution and must therefore involve principally the phenoxide ion; on the other hand, in the peroxidase oxidation of *p*-cresol recently reported by Westerfeld and Lowe (1942), which takes place at pH 6·5 and leads to the same products as those obtained by Pummerer, the reactant must be the phenol itself. Since the reaction with which we are chiefly concerned, not only as it is conducted in the test-tube but as it must occur *in vivo*, undoubtedly involves phenoxide ions, for the rest of this discussion we shall proceed as if we were dealing with dissociated phenolic groups.

If now we assume the oxidation of a *p*-substituted phenoxide ion to consist in the removal of one electron from the lone pair on the oxygen of form *A* and from the *p*- and *o*-carbons respectively of forms *B* and *C*, we get three corresponding free radicals *D*, *E*, and *F*, and we may consider the probabilities of reaction between these forms and the nature of the products which would arise therefrom.



D *E* *F*

Self-interaction of *D* would lead to a diphenyl peroxide structure; even if this were isolable, we may judge from Pummerer's work that it would be very unstable. Self-interaction of *E* would lead to a dicyclic ketone (VI); no compounds of this precise type are known, although there are no steric factors which would preclude their formation. The nearest analogy seems to be cyclic ketones of type (VII) which were obtained by Auwers and Keil (1902) as by-products in the Reimer–Tiemann reaction applied to *p*-alkylated phenols.



(VI.) (VII.)

Neither Pummerer nor Westerfeld and Lowe isolated a compound of type (VI) from the oxidation of *p*-cresol; this may be explained either by the impossibility of formation of such a compound or by its polymerisation, if formed, to give unrecognisable products. The same general considerations apply to interaction between *E* and *F*. Self-interaction of *F* can occur and would lead, where R = CH_3, to 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl, a compound which, as we have already seen, was obtained both by Pummerer and by Westerfeld and Lowe. Repetition of this interaction would lead to the corresponding terphenyl derivative, which has

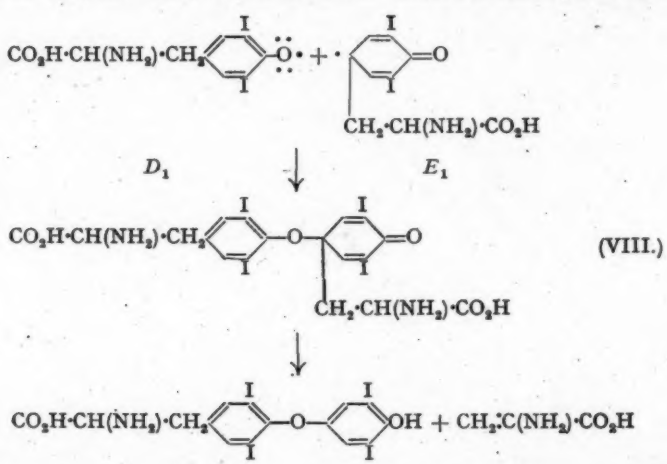
also been identified by Westerfeld and Lowe among the products of oxidation of *p*-cresol by peroxidase, and was isolated but not identified by Pummerer.

Interaction of *D* and *E* would give the intermediate compound which (where R = CH_3) rearranges to the ketonic tetrahydrobenzofuran obtained by Pummerer as already described.

Interaction of *D* and *F* should lead to an isomeric ketonic tetrahydrobenzofuran which has not been isolated.

It is thus seen that, of the three compounds which would be predicted on this theory as arising from the oxidation of *p*-cresol, two have actually been obtained.

If we now transfer these ideas to a phenol which is not only substituted in the *p*-position but also carries substituents in both *o*-positions, *i.e.*, to such a phenol as di-iodotyrosine, we find that the probabilities of interaction of the various forms are more limited. In addition to the limitations already noted, self-interaction in the *o*-position will be inhibited by the presence of the iodine atoms, so that the formation of a diphenyl is not to be expected. We are left, therefore, with interaction between forms D_1 and E_1 as the most probable



(VIII.)

course of events and this is precisely the reaction postulated by Johnson, leading to the intermediate compound (VIII): this, as already pointed out, being unable to undergo the rearrangement to a tetrahydrobenzofuran because of the presence of the iodine atoms *ortho* to the phenolic group, can only rearrange itself in another way, namely, by loss of one side chain as dehydroalanine, leading to ammonia and pyruvic acid or to serine.

Theoretical reasoning therefore not only demonstrates a possible mechanism for the oxidative coupling of two molecules of di-iodotyrosine to give thyroxine, but suggests that such a reaction is rendered more likely by the presence of the iodine atoms in the former compound. Objective evidence in favour of the reaction mechanism which has been postulated might be more readily forthcoming if conditions for the oxidation could be devised more favourable than any which we have yet discovered. Such objective evidence of an important character would be provided by the unequivocal recognition of the lost side chain in the form either of serine or of pyruvic acid; under the conditions of our experiment, however, both of these products, if formed, would be largely destroyed, and up to the present we have not been able to demonstrate their presence.

The excuse for the speculation in which I have indulged in the latter part of this lecture is that, in my view, it indicates the directions in which we may profitably seek for the explanation of the mechanism of a somewhat obscure reaction, which is interesting not only to the organic chemist but also to the biologist who desires to understand the details of an important biosynthetic process.

The development of the theoretical arguments in this lecture owes much to discussion with my colleague, Dr. A. Neuberger, to whom I wish to express my gratitude.

REFERENCES.

Abelin, A. (1934) *Klin. Woch.*, **13**, 940.
Abelin, A. (1934) *Arch. Exp. Path. Pharmacol.*, **173**, 146.
Abelin, A. (1934) *Ibid.*, **175**, 151.
Abelin, A. (1936) *Ibid.*, **181**, 250.
Abelin, A. and Florin, A. (1933) *Ibid.*, **171**, 433.
Abelin, A. and Neftel, A. (1938) *Ibid.*, **189**, 473.
Auwers, K. and Keil, G. (1902) *Ber.*, **35**, 4207.
Block, P. (jun.). (1940) *J. Biol. Chem.*, **135**, 51.
Canzanelli, A., Harington, C. R., and Randall, S. S. (1934) *Biochem. J.*, **28**, 68.
Harington, C. R. (1926) *Ibid.*, **20**, 300.
Harington, C. R. (1928) *Ibid.*, **22**, 1429.

Harington, C. R. and Barger, G. (1927) *Biochem. J.*, **21**, 169.
Harington, C. R. and Neuberger, A. (1936) *Ibid.*, **30**, 809.
Harington, C. R. and Pitt-Rivers, R. V. (1939) *Nature*, **144**, 205.
Harington, C. R. and Randall, S. S. (1929) *Biochem. J.*, **23**, 373.
Harington, C. R. and Salter, W. T. (1930) *Ibid.*, **24**, 456.
Herriott, R. (1941—2) *J. Gen. Physiol.*, **25**, 185.
Johnson, T. B. and Tewkesbury, L. B. (jun.). (1942) *Proc. Nat. Acad. Sci.*, **28**, 73.
Leland, J. P. and Foster, G. L. (1932) *J. Biol. Chem.*, **95**, 165.
Ludwig, W. and von Mutzenbecher, P. (1939) *Z. physiol. Chem.*, **258**, 195.
Mann, W., Leblond, C. P., and Warren, S. L. (1942) *J. Biol. Chem.*, **142**, 905.
Morton, M. E. and Chaikoff, I. L. (1943) *Ibid.*, **147**, 1.
von Mutzenbecher, P. (1939) *Z. physiol. Chem.*, **261**, 253.
Neuberger, A. (1934) *Biochem. J.*, **28**, 1982.
Oswald, A. (1910) *Z. physiol. Chem.*, **70**, 310.
Pauly, H. (1910) *Ber.*, **43**, 2243.
Perlman, I., Chaikoff, I. L., and Morton, M. E. (1941, a) *J. Biol. Chem.*, **139**, 433.
Perlman, I., Morton, M. E., and Chaikoff, I. L. (1941, b) *Ibid.*, p. 449.
Pummerer, R. (1919) *Ber.*, **52**, 1403.
Pummerer, R. and Cherbuliez, E. (1914) *Ber.*, **47**, 2957.
Pummerer, R. and Cherbuliez, E. (1919) *Ber.*, **52**, 1414.
Pummerer, R. and Frankfurter, F. (1914) *Ber.*, **47**, 1472.
Pummerer, R., Melamed, D., and Puttfarcken, H. (1922) *Ber.*, **55**, 3116.
Pummerer, R., Puttfarcken, H., and Schopflocher, P. (1925) *Ber.*, **58**, 1808.
Pummerer, R. and Rieche, A. (1926) *Ber.*, **59**, 2161.
Reineke, E. P. and Turner, C. W. (1942) *Research Bull. Univ. Missouri*, No. 355.
Schachner, H., Franklin, A. L., and Chaikoff, I. L. (1943) *J. Biol. Chem.*, **151**, 191.
Westerfeld, W. W. and Lowe, C. (1942) *Ibid.*, **145**, 463.

OBITUARY NOTICES.

GEORGE GERALD HENDERSON.

1862—1942.

If the story of George Gerald Henderson be told merely as a chronological record, there would remain for our successors an imperfect picture of a very remarkable man. He was a Scot, and received his scientific education at the University of Glasgow; in succession he held a Lectureship and two Professorships of Chemistry in his native city and he died full of years in the land he loved. The story as thus told suggests that his life's work was spent in a limited sphere, but that is true only in a geographical sense, for his influence spread far afield and he was in his day recognised as one of the most prominent figures in British Chemistry. It will be generally conceded that the period when the nineteenth century merged into the twentieth was a critical time in the development of science in this country. Opportunities for scientific education were expanding rapidly, facilities for original research were becoming more widely available, and the investigator was no longer a solitary worker. These were profound changes and no country—least of all a small country such as Scotland, firmly wedded to long-established educational tradition—could take a profitable part in what we must regard as an educational revolution, in the absence of wise scientific leadership. That rôle was played by G. G. Henderson and he played it supremely well. While it is a pious duty, willingly undertaken, to pay tribute to his life's work, it is difficult for me to speak freely of him as a man, for I was bound to him by ties closer than those which usually link master and disciple. Nearly half a century ago it was my lot to sit each morning in the bleak Chemistry Lecture Theatre of the old Andersonian Institute in Glasgow and thereafter to spend most of the day at toilsome quantitative separations in a depressing laboratory. It is not merely the passage of the years which has softened the memory of many discomforts then endured and has left a permanent impression of happiness; for even as young and callow students we were conscious that we were led by one who, without his seeking, had gained the honour of winning from youth something which approached hero-worship. No doubt we worked enthusiastically at our Chemistry because of interest in the subject, but we did so in greater measure to reap the reward of our Professor's commendation. He did not attain this position through cultivating the good-will of students by over-indulgence; indeed the reverse was the case, and while his words of praise were few, he never shirked the stinging rebuke due to those who failed to give of their best. Instinctively he knew when, where and how to encourage, or if need be, to blame. I am not alone in looking back to the early days of Henderson's first professorship with more than mere appreciation; although now a dwindling band, his old students of the 1890's still remember gratefully what they owe to the influence of a great teacher.

The path he had climbed to reach a Professor's Chair at the early age of thirty was not easy, and his adoption of a scientific career cannot be explained in terms of heredity or environment. Born on January 30th, 1862, the second son of a Glasgow merchant, he could claim descent from a long line of Kinross-shire lairds. Church and State had each made their contributions to his inheritance, but no trace is to be found of scientific influences, and his early education, pursued at a private school, was based largely on Classics and Mathematics and followed orthodox lines. Nevertheless, when he entered the University of Glasgow at the impressionable age of fifteen and a half, he broke away from school and family tradition and embarked on the study of Science in place of submitting himself to the customary discipline of the Liberal Arts. Mathematics, Physics, Chemistry, Geology, Botany, and Zoology composed the strenuous curriculum of the period; the course was obviously designed to give a broad scientific education rather than to produce specialists, but Henderson had not reached his twentieth birthday when he graduated B.Sc. " with Distinction " in Chemistry and had published his first paper on the formation of serpentine from dolomite. Reversing the usual order of study, he then proceeded to complete the Arts degree, his seven pillars of wisdom being Latin, Greek, English, Logic, Moral Philosophy, Mathematics, and Natural Science. In these studies he displayed his versatility and acquired delicate scholarly tastes which never forsook him—there are few Professors in our generation who were Prizemen in both Greek and Chemistry.

He was now firmly pledged to science and he brought to bear on his special study a well-nourished mind. Recognising that the training in Glasgow was deficient in Organic Chemistry and in the new Physical Chemistry, Henderson proceeded to Leipzig, where in successive Long Vacations he extended his studies and commenced organic research under the direction of Wislicenus. In the leisurely days of last century the Long Vacation, extending as it did from March to October, was worthy of the name and it was thus possible for young Henderson to divide the academic year into two equal parts. The first half was spent in the University of Glasgow as a Lecturer and Demonstrator teaching Inorganic Chemistry and Mineralogy, while in the second half he made himself increasingly efficient as a student of Organic Chemistry in the famous Institute in the Liebigstrasse. The fruits of this strenuous preparation matured rapidly and his subsequent publications on synthetical uses of malonic ester and acetoacetic ester reflected the inspiration of Wislicenus on this zealous pupil. One of these modest papers is worthy of special mention, for, as long ago as 1889, Henderson described the action of chromium oxychloride on pinene and directed attention to the use of a reagent which was destined in his hands to give valuable results in future work. It was appropriate that academic promotion should follow quickly, and the opportunity to offer him independent status as a Lecturer came in 1889 when he was

appointed to Queen Margaret College, Glasgow. In the movement which resulted in the admission of women students to the Scottish Universities, Glasgow played a leading part and at first adopted the policy of providing special classes and a separate College for women. There for three years Henderson developed his teaching powers, and continued, under severe difficulties, his researches on topics in which the influence of Wislicenus, if still discernible, is faint. In 1892 he was called to succeed Dittmar as Freeland Professor of Chemistry in what was then known as the Glasgow and West of Scotland Technical College. The locus of the Chair was the Andersonian Institute, a massive building not without a certain architectural dignity but peculiarly unsuitable as a school of experimental sciences. Cramped quarters, and an almost total lack of ventilation were ill-adapted for the complex quantitative analyses which formed the basis of student instruction, but on the other hand the balances and instruments of precision were excellent, and quantitative accuracy was the key-note of the training. The allegiance of Chemistry to Mineralogy still survived and Henderson wisely made no attempt to interfere with the Dittmar tradition that practice in analysis is the best introduction to Chemistry—well-thumbed copies of Fresenius were to be found in most of the benches—but he extended the exercises in Organic Chemistry, gradually introduced Physical Chemistry, and in the end provided courses which would be recognised even to-day as highly efficient. At that date there was no examination for entrance to the College and, in consequence, great variation existed in the quality of the students, who for the most part were preparing themselves as analysts or works chemists. This fact placed a heavy burden on the Professor, who of necessity had to adapt his lectures to the capacity of his audience and at the same time to prepare the best of his students for the degree examinations of London University. Henderson accomplished this difficult task with masterly skill. Unlike some of his colleagues in other departments, he found no difficulty in maintaining discipline, for in his presence the most turbulent students quailed and over-exuberance wilted. Above average height, slim, well-tailored and athletic (reputedly he was the first man to skate from Balloch to Luss when Loch Lomond was frozen in the Great Frost of 1894), he commanded attention from the moment the lecture started. He used few notes, his experiments were performed with dexterity and were arranged with an eye to artistic effect, the blackboard illustrations were elegantly written, and the most complex equations always balanced. Whether or not he had consciously adopted Spurgeon as his model, the fact remains that his opening and closing sentences were always carefully prepared and were calculated to arrest immediate attention and to carry interest forward to the succeeding lecture. It all seemed so natural and spontaneous that it came as a surprise in after years to learn that this smooth technique of teaching was the product of much study and careful practice. Equally it was surprising to realise that the professorial dignity with which he carried himself was a cloak to cover a measure of shyness.

In the laboratory, he gave the impression that the case of each individual student was the Professor's special care. Following a time-table, the underlying system of which we never fully discovered, so that his visits came on unexpected and sometimes inconvenient occasions, he made his daily rounds and impressed on each of us that accurate working can only be conducted on a tidy bench. His own bench certainly conformed to his high standard of neatness and there in his scanty leisure (there were evening classes as well as day classes) he worked on the formation of compounds analogous to tartar emetic. These researches reflect his earlier association with the Medical School at Glasgow, and the influence of van 't Hoff was also apparent in his studies on the optical effect induced in lactic acid by reaction with metallic oxides; but a more striking divergence in research interests was due to his growing friendship with Dr. (afterwards Sir George) Beilby. The problem of investigation in which they collaborated had originated in the technical difficulty of finding a metal suitable for conducting a current of ammonia at high temperatures, and the source of the trouble was traced to the alternate formation and decomposition of the corresponding metallic nitride. This led to a general study of nitrides, and the resulting publication is not only a model of its kind but is also a striking example of the labour and ingenuity necessary for the solution of such problems before the adoption of purely physical methods greatly simplified the procedure. Other researches on analytical topics likewise revealed his allegiance to inorganic chemistry; but in 1903 there appeared the first of his papers on the terpenes, a task he never laid down until his research days were done. Of some seventy publications which bear his name, about half are concerned with terpene problems: these papers, to which detailed reference will be made later, appeared in steady succession over a period of thirty years, even at times when he was heavily engaged with other duties.

Despite increasing invasion of his time, Henderson never forsook the research bench and his story provides yet another example of how scientific zeal cannot be extinguished by the exacting claims made on Professors who are unfortunate enough to possess a capacity for business affairs coupled with a sense of public duty. " Never allow yourself to become a Committee man," was advice he often gave to his pupils, and although he himself broke the rule he did so with full knowledge of the sacrifices involved.

Recognition that the Technical College of Glasgow was worthy of buildings appropriate to its purposes and achievement was slow in maturing, but in the end the idea was magnificently realised and Henderson gave invaluable help in carrying out the great building scheme. But he had not long enjoyed the facilities of his new laboratories when the call came to him in 1919 to return to the University of Glasgow as Regius Professor of Chemistry—his path of progress was cyclic, and so far as the Royal Technical College was concerned, he had " found Rome brick and left it marble." His entry into the University Chair coincided with the return of soldier students from the Four Years War, and Henderson brought all his fine qualities of heart and mind to the fulfilment of the duty of mending broken careers. Classrooms were overcrowded; teachers

were overworked and students were overstrained; but in the midst of this confusion there was the quiet controlling force of a Professor who never seemed to weary and who never lost his cheerful outlook on life. At this period, the claims of other duties were increasing; he acted as Dean of the Faculty of Science and as an Assessor on the University Court. Outside his University work he had for many years been an active member of the British Association and had worked his way up to the Presidency of Section B, where his address may be regarded as the first serious attempt to trace the effect of the scientific revolution on the early history of chemical industry in Scotland. Similarly, his activity on the Councils of the Society of Chemical Industry and the Institute of Chemistry was recognised by his call to the President's Chair of each of these bodies. There remained one further honour which was his as of right—the Presidency of the Chemical Society—and this came to him in 1931, by which date he had been a Fellow of the Society for 46 years. The frequent journeys to London imposed a considerable strain on an overworked man of seventy, but there can be no doubt that Henderson greatly enjoyed his tenure of the President's office and he often spoke in terms of sincere appreciation of the way in which everything was done to ease his burden. He presided at meetings with a due sense of the dignity belonging to the leadership of a Learned Society; his bearing was in no sense austere and he knew how to put new members at their ease, infusing into the most diffident young chemist the spirit of fellowship which is, or ought to be, the essence of a scientific community.

Intermingled with this strenuous programme he gave eight years of earnest thought to the scheme of providing a Chemistry Institute worthy of the University of Glasgow. The large capital sum required was ultimately forthcoming, and Henderson, for the second time in his life, devoted himself to the problems of architectural planning. Only when he felt that the task had reached a stage where final details should be left to his successor did he seek the leisure he had earned so well, and in 1937 he resigned from his Chair.

In his round of ceaseless activities he was sustained by the serene happiness of his home life and the loving care of his wife. In 1895, soon after his appointment to the Freeland Chair, he married his cousin, Agnes Mackenzie Kerr, and for more than forty years she made his life glad, welcoming colleagues and students round the study fire, accompanying her husband on his travels, sharing his interest in music and joining annually in the fishing expeditions to the Outer Hebrides. The fact that they remained childless served to make more active a close companionship which was broken with tragic suddenness. Their intention was to retire to the Isle of Harris, which had been the scene of many a happy fishing holiday, and Mrs. Henderson was preparing their island home for the arrival of her husband when death overtook her without warning. So it was a tired broken-hearted man who said good-bye to his Chemistry and sought consolation in scenes hallowed by precious memories and in the company of simple islanders who made him welcome in their midst. The time of waiting was not long, and on September 28th, 1942, Henderson passed away, suddenly, as was his desire. It does not need the confirmation of his letters to convince me that many a time in his solitude he looked back with quiet pleasure on the opportunities which had come to him to serve science faithfully and well. Honours were not denied him; he was elected a Fellow of the Royal Society in 1916, received Honorary Degrees from St. Andrews, Glasgow, and Belfast, and was awarded the medal of the Society of Chemical Industry. Despite his inherent modesty these marks of public recognition were welcome to him, but more and more his thoughts turned to his former students and colleagues. There were many of them who had won their way to responsible positions, among them, Professors I. M. Heilbron, A. Robertson, A. R. Todd, W. R. Boyd, M. A. Parker, F. J. Wilson, and W. R. Lang. But there is also that wider circle of men and women scattered over the world who are doing good work and doing it all the better through the example he set before them and as a result of the scientific training received at his hands. Science in Scotland is poorer by the passing of George Gerald Henderson; but his work and worth will not be forgotten, and his name will be held in affectionate remembrance in our generation.

J. C. Irvine.

The following account of Henderson's researches on the terpenes has been contributed by Dr. J. L. Simonsen, F.R.S., to whom I am much indebted.

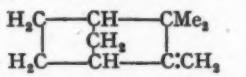
J. C. I.

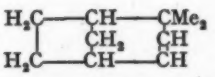
In 1889 in a short paper (J., **55**, 45) Henderson reported the results of some preliminary experiments on the oxidation of α-pinene with chromyl chloride. He returned to this subject some ten years later and thus opened a field of research which was to form the main interest of the Glasgow Laboratories for the next thirty years. When this work was commenced, the chemistry of the terpene hydrocarbons was still in a very confused state and Henderson clearly thought that our knowledge might be advanced by a study of their interaction with some of the less powerful oxidising agents such as chromyl chloride, hydrogen peroxide, and hypochlorous acid.

Étard (*Compt. rend.*, **1893**, **116**, 434) had observed that α-pinene and camphene on oxidation with chromyl chloride gave an aldehyde, $C_{10}H_{14}O$, from which an acid, $C_{10}H_{14}O_2$, could be prepared, whereas according to Bredt and Jagelki (*Annalen*, **1899**, **310**, 113) camphene gave with this reagent camphenilanaldehyde, $C_{10}H_{16}O$, and camphenilanic acid, $C_{10}H_{16}O_2$, which isomerised readily to *iso*camphenilanic acid. Although Henderson himself did not investigate the oxidation of camphene with chromyl chloride, as will be seen later he gave considerable attention to the products described by Bredt and Jagelki.

With Gray and Smith (J., 1903, **83**, 1299) and with Heilbron (J., 1908, **93**, 1299) he showed that α-pinene

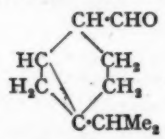
gave on treatment with chromyl chloride in carbon disulphide solution a substance $C_{10}H_{16}{,}2CrO_2Cl_2$, decomposed by water to yield an aldehyde, $C_{10}H_{16}O$, and a ketone, $C_9H_{14}O$, together with a chloro-compound, $C_{10}H_{15}OCl$. The structure of these degradation products was not elucidated, but it is highly improbable that they contain either a pinane or a camphane ring structure. Many years later, in collaboration with Chisholm (J., 1924, **125**, 106), he found that the ketone was formed also by the oxidation of β-pinene with chromyl chloride, although the other products were different and the only one identified was *trans*pinolglycol (Wagner and Slawinski, *Ber.*, 1899, **32**, 2072). The oxidation of bornylene with chromyl chloride (with Heilbron, J., 1911, **99**, 1887) proceeded more smoothly, yielding a chloro-ketone, $C_{10}H_{15}OCl$, from which camphoric acid was obtained on oxidation. This chloro-ketone, since it is not identical with either of the isomeric α-chlorocamphors, subsequently described by Lowry and Steele (J., 1915, **107**, 1382), is probably a chloro*epi*camphor. Other products of the oxidation were camphenilanaldehyde and *iso*camphanilanaldehyde. Henderson and Heilbron during the course of this research studied also the action of nitrous and nitric acids on bornylene. By the action of the former reagent bornylene nitrosite was prepared, and by the action of nitric acid dinitrocamphane was obtained. As a result of this investigation Henderson and Heilbron (J., 1911, **99**, 1901) were led to discuss in an interesting theoretical paper the structure of camphene, for which at that time the formulæ (I) and (II) were under consideration.

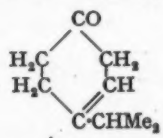
(I.) 

 (II.)

In this admirable contribution they advanced cogent evidence in support of (I) and they suggested, apparently for the first time, that the abnormal results obtained on the oxidation of camphene with potassium permanganate may have been due to the alkalinity of the solution in which the oxidation was carried out. This suggestion was subsequently confirmed by Langlois (*Ann. Chim.*, 1919, **12**, 301).

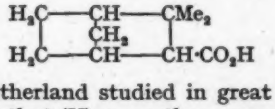
With Robertson and Brown (J., 1922, **121**, 2717; 1924, **125**, 265) the oxidation of sabinene with chromyl chloride was studied and was found to give sabinenaldehyde (III) and Δ^1-*iso*propyl*cyclo*hexen-4-one (IV).

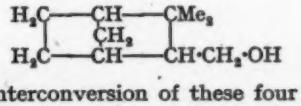
(III.) 

 (IV.)

The first action of chromyl chloride on monocyclic terpenes would appear to be their dehydrogenation to *p*-cymene, since it was found (J., 1907, **91**, 1871; with Cameron, J., 1909, **95**, 969) that both limonene and α-terpinene gave α-*p*-tolylpropaldehyde and *p*-tolyl methyl ketone, products identical with those obtained by the reaction of this reagent and *p*-cymene (Errara, *Gazzetta*, 1889, **19**, 528; 1891, **21**, 76; Miller and Rohde, *Ber.*, 1890, **23**, 1070; 1891, **24**, 1356).

In another series of papers the oxidation of the dicyclic terpenes α- and β-pinenes, camphene, and bornylene with hydrogen peroxide was described (with Sutherland, J., 1910, **97**, 1616; 1912, **101**, 2288; 1914, **105**, 1710; with Caw, J., 1913, **103**, 1543; with Chisholm, J., 1924, **125**, 107). With α- and β-pinenes, only the usual hydration products, α-terpineol, borneol, and fenchyl alcohol, were obtained, but results of greater interest were observed with camphene and bornylene. Oxidation of camphene resulted in the formation of camphene glycol, camphenilone, *iso*camphenilanaldehyde, an isomeride of camphenilanaldehyde (V), and camphenanic acid. Peculiar interest attaches to this acid, m. p. 95°, since it can be isomerised to *iso*camphenanic acid, m. p. 74°. These two acids are isomeric also with the camphenilanic acid, m. p. 65°, and *iso*camphenilanic acid, m. p. 118°, prepared originally by Bredt and Jagelki (*loc. cit.*) by the oxidation of camphene with chromyl chloride. Bredt (*Annalen*, 1909, **366**, 57) assigned to these acids the structure (V).

(V.) 

 (VI.)

Henderson and Miss Sutherland studied in great detail the interconversion of these four acids, and, whilst there can be little doubt that (V) correctly represents camphenilanic and *iso*camphenilanic acids, the relationship of these four acids to one another is still obscure, since their esters give on reduction the same alcohol, camphenilanol (VI). Camphenanic and *iso*camphenanic acids are formed also by the oxidation of bornylene with hydrogen peroxide. A convenient method for the preparation of this hydrocarbon in the pure state was described by Henderson and Caw (J., 1912, **101**, 1416).

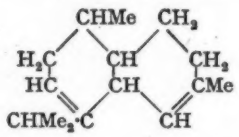
A brief reference may be made also to three papers (with Heilbron and Howie, J., 1914, **105**, 1367; with Marsh, J., 1921, **119**, 1492; with Kerr, J., 1924, **125**, 102) on the action of hypochlorous acid on α- and β-pinene and on camphene. With the former hydrocarbons ring fission occurs with the formation of dichlorohydroxymethanes; from camphene a chloro*iso*borneol is obtained.

Influenced doubtless by his interest in catalysis, Henderson synthesised also some *p*- and *m*-menthadienes (with Sutherland, J., 1910, **97**, 1616; with Boyd, J., 1911, **99**, 2159; with Schotz, J., 1912, **101**, 2563; with Smeaton, J., 1920, **117**, 144). Since the structures of these hydrocarbons were not determined, it will suffice to illustrate this aspect of Henderson's work by one example. Thymol was catalytically hydrogenated by the

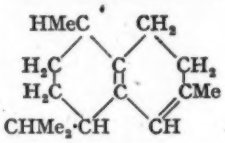
Sabatier–Senderens process to menthol, from which by dehydrogenation Δ^3-menthene was prepared. This on treatment with bromine gave a dibromide, from which by the action of alkali $\Delta^{2:4}$-*p*-menthadiene was obtained.

About 1924, Henderson entered the field of sesquiterpene chemistry. Here his attention was directed mainly to the hydrocarbons cadinene and the caryophyllenes. He found with A. Robertson (J., 1924, **125**, 1992) and with J. M. Robertson (J., 1926, 2811) that cadinene could be isomerised readily to *iso*cadinene, for which on the basis of the then accepted α-cadinene formula (VII) the structural formula (VIII) was suggested.

(VII.)

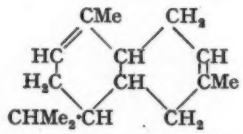


(VIII.)

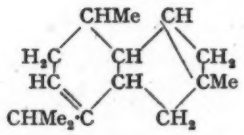


The formula for cadinene (IX) now advanced (Campbell and Soffer, *J. Amer. Chem. Soc.*, 1942, **64**, 417) makes this isomerisation equally readily explicable.

(IX.)



(X.)



As Henderson and Robertson point out, *iso*cadinene is identical probably with a hydrocarbon isolated by Troger and Feldmann (*Arch. Pharm.*, 1898, **236**, 692) and by Lepeschkin (*J. Russ. Phys. Chem. Soc.*, 1908, **40**, 26) from oil of cade. Incidental to this investigation was the separation from the supa-oil (from *Sundora Wallichii*) of the hydrocarbon copaene (with McNab and Robertson, J., 1926, 3077). Since copaene is stated to give cadinene dihydrochloride on treatment with hydrogen chloride, it can probably no longer be represented by (X) and this new source of the hydrocarbon may render possible a reinvestigation of its structure. Henderson's final publications (with Robertson and Kerr, J., 1926, **62**; with McCrone and Robertson, J., 1929, 1368; with Bell, J., 1930, 1971) were concerned with the chemistry of the caryophyllenes. Perhaps the most important contributions which he made were the observations that whereas α-caryophyllenic alcohol on dehydration gave solely clovene and on oxidation the crystalline acid, clovenic acid, the β-alcohol gave a mixture of clovene and *iso*clovene on dehydration and a liquid acid on oxidation.

ARTHUR AVERY READ.

1868—1943.

Prof. A. A. Read died on September 24th, 1943, at Bournemouth, where he had lived after his retirement from the Chair of Metallurgy at the University College of South Wales and Monmouthshire, Cardiff. He was born at Honiton, Devon, in 1868 and was educated at Exeter Grammar School, Owens College, Manchester, and at Sheffield University—then the Technical College—where he studied metallurgy under the late Prof. J. O. Arnold, F.R.S. He qualified as A.I.C. (1889) and F.I.C. (1895) and was subsequently awarded the degrees of M.Met. and D.Met. by the University of Sheffield. He went to Cardiff in 1894 as the first Lecturer in Metallurgy, and later, when metallurgy had been constituted as a separate department, was appointed the first Professor.

Read was the pioneer of metallurgical education in Wales. His enthusiasm was such that the new department flourished. He obtained University recognition for an Applied Science degree with metallurgy as the principal subject and thus, in 1903, had the distinction of having trained the first student in Great Britain to obtain the degree of B.Sc. in metallurgy. Before his retirement in 1933 he had fulfilled his ambition to establish a department worthy of the University of Wales, housed in a modern and well-equipped building which had been erected with the financial assistance of the Monmouthshire and South Wales Coal Owners' Association.

Read realised that the University had a two-fold obligation, not only to teach but also to prosecute original research, and he managed to keep an even balance between the two while at the same time he worked hard to build and equip his department. His work in collaboration with Arnold on the chemical and mechanical relations of iron, carbon and certain alloy elements in steel was published over a period of years from 1894 to 1915 and was an important contribution to the development of modern alloy steels. Following the lead of Abel and others (who used solution methods), Arnold and Read in 1894 devised the electrolytic method of separating Fe_3C from steel and later adapted it to the investigation of carbides occurring in alloy steels. It was with this aspect of the joint work that Read was primarily concerned. It is now generally agreed that analytical data regarding the composition of residues obtained by chemical attack should be used with caution in drawing conclusions as to the constitution of the carbides present in a steel. Nevertheless there were several instances in which carbides isolated by Arnold and Read showed the characteristics of a definite compound, *e.g.*, Cr_4C, V_4C_3, WC. The presence of these in steel has since been confirmed by *X*-ray analysis,

as also has the isomorphous replacement of iron in Fe_3C by manganese, cobalt, or nickel revealed by Arnold and Read's work, which thus remains a sound check on the constitution assigned to slowly cooled steels containing about 0·6 to 0·9% of carbon in the ternary equilibrium diagrams of carbon, iron, and another metal.

Read's interest in non-ferrous metallurgy resulted in the publication of several papers in the *Journal* of the Institute of Metals, 1915—1922, dealing with alloys of nickel, aluminium, and copper. The work on alloys containing 90% of copper with varying amounts of aluminium and nickel revealed one of the first recorded instances of " precipitation hardening " in copper-rich alloys.

Outside his college work Read was interested chiefly in the Volunteers and the Territorials, in which he held a commission for more than 25 years, receiving the Territorial Decoration. During the last war he was away from College on military service. After the war, the University of Wales and the College at Cardiff, both young institutions, were faced with serious problems, and Read sacrificed his personal inclination to resume his researches and applied himself energetically to University affairs. He brought to bear on academic matters an administrative outlook which was of inestimable value. His work was recognised by the University by conferring on him the degree of D.Sc. *honoris causa*, and the title of Emeritus Professor.

At first contact, Read was a little awe-inspiring to students entering his department, but he quickly won their confidence and respect, which ripened into affection under the influence of his kindly and genial disposition. To the students of the College as a whole he was a very good friend, always ready to champion their interests and to help on a good cause.

R. H. Greaves.
W. R. D. Jones.

JAMES McCONNELL SANDERS.

1875—1944.

James McConnell Sanders went to Mexico in 1901, where he became Chief Chemist to the Mexican Customs, Head of the Research Department of the Government Medical Institute, and later Professor of Chemistry in the University of Mexico.

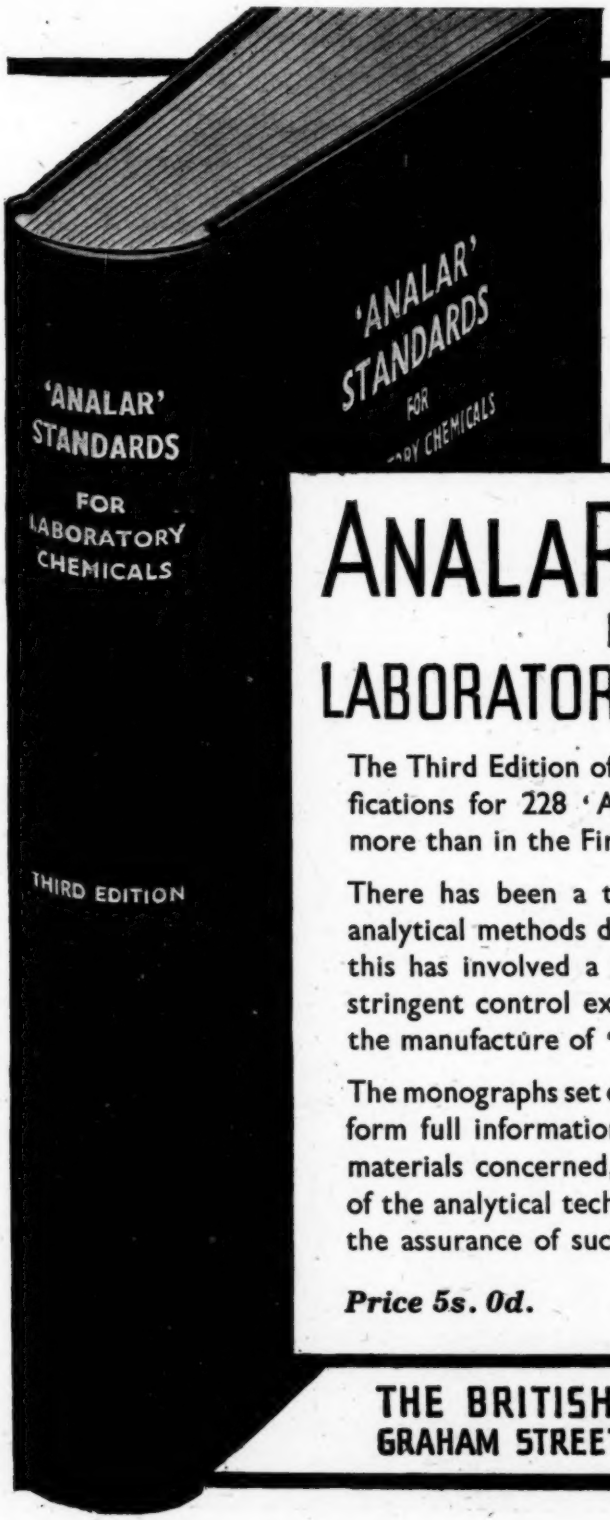
In 1915 he joined the Mexican Eagle Oil Co. as Chief Chemist to their refineries. In 1918 he returned to London and joined the Mexican Department of the Anglo-Saxon Petroleum Co. as chemical adviser. During the last three years before he retired he occupied the position of general consultant to the Shell Laboratories. In this position he was the more able to carry on with the study of the microchemistry of crude petroleum, a subject in which he had always taken a great interest, and which he had made his hobby.

He was a skilled manipulator and a good glass-blower and took a great pride in making his own apparatus, much of which was of an original type. His botanical knowledge was of great assistance to him in his microscopic examination of the residual dust obtained from various crude petroleums, from which he was able to draw conclusions as to the mother-substance of the petroleums which he examined.

He published a paper on " The Microscopical Examination of Crude Petroleum " in the *Journal* of the Institute of Petroleum in 1937.

He retired in 1939, but retirement for him meant the transfer of his laboratory to his own home, where he carried on until his death the work which was his much-loved hobby.

J. Kewley.



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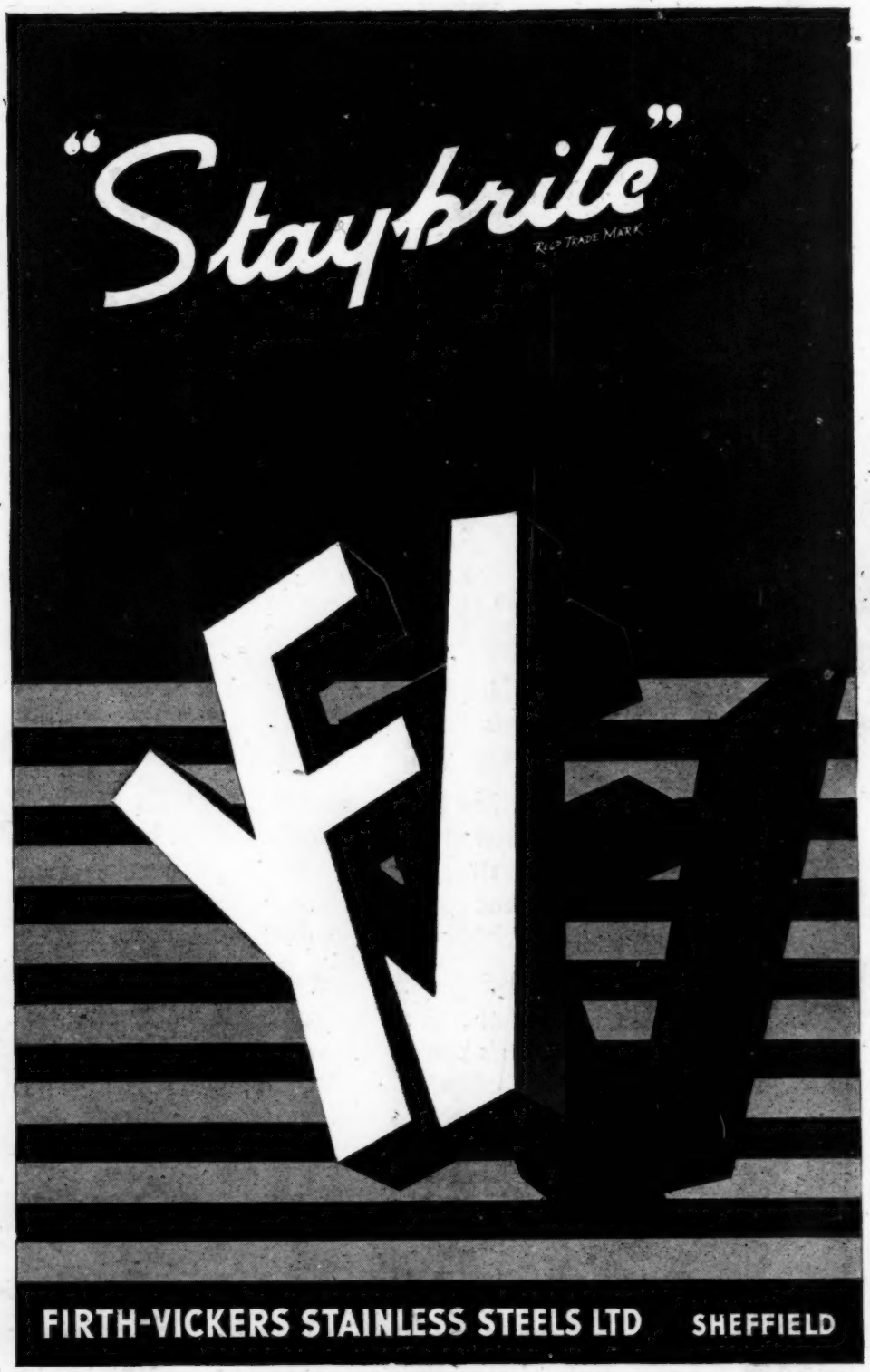

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